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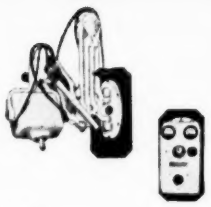

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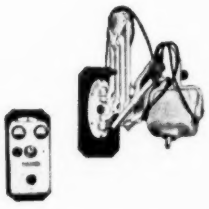

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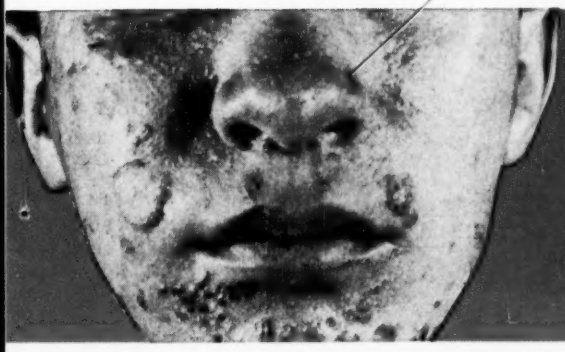
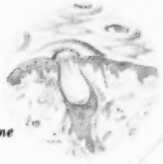
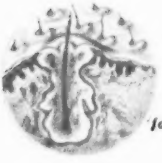


skin infections and antibiotics


acne

pyoderma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1. *Bednar, G. A.: South. M. J. 46:298 (March) 1953.*
2. *Wright, C. S., et al.: A. M. A. Arch. Dermat. & Syph. 67:125 (Feb.) 1953.*
3. *Robinson, H. M., et al.: South. M. J. (in press).*
4. *Andrews, G. C., et al.: J. A. M. A. 146:1107 (July 21) 1951.*

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References:

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2. Stieglitz, E. J.: Geriatric Medicine, p. 848, 1943.

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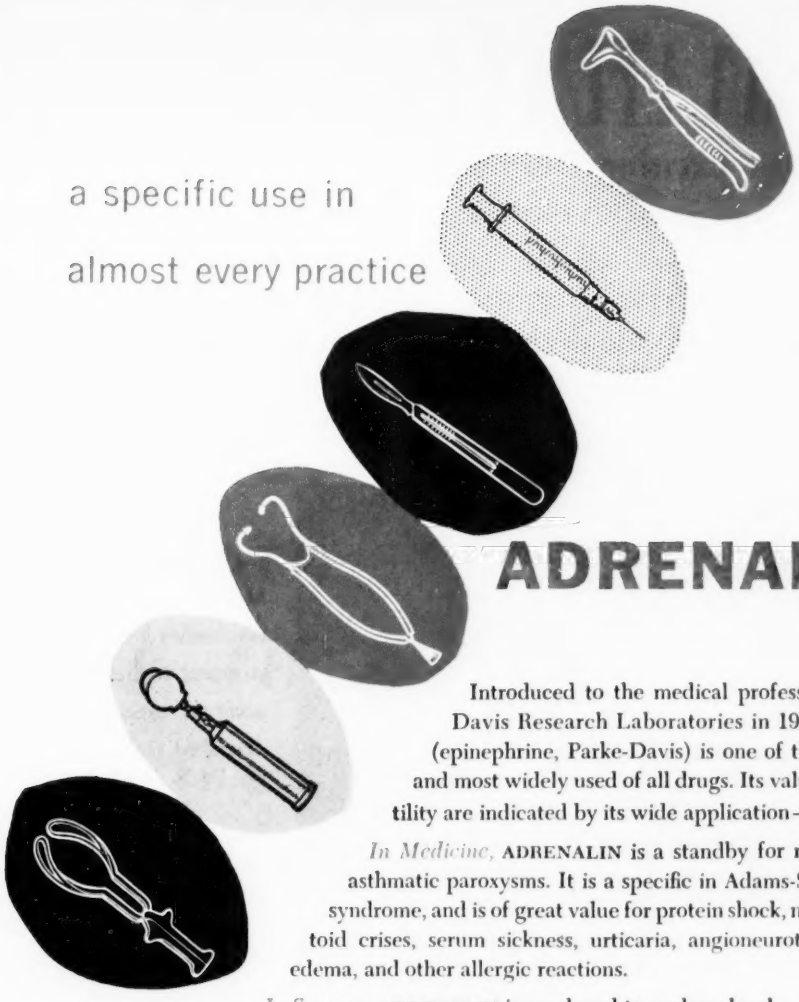

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Archives of Dermatology and Syphilology

VOLUME 68 DECEMBER 1953 NUMBER 6

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ATOPIC DERMATITIS

A Study of Its Natural Course and of Wool as a Dominant Allergenic Factor

EARL D. OSBORNE, M.D.
AND
PHILIP F. MURRAY, M.D.
BUFFALO

KNOWLEDGE of the natural history of atopic dermatitis, whether treated or untreated, is important. This includes an understanding of what is apt to happen in dermatitis from infancy to mature adult life. In evaluating any method of treatment, the natural course of the disease for the age period of the group studied must always be considered. With these points in mind, we recently completed a comprehensive study of the records of more than 2,500 patients from 2 weeks of age to late adult life.

We have summarized our findings as follows.

In dermatologic practice, in approximately 30 to 40% of the cases dermatitis in infants under 1 year of age was due to external sources of primary irritation and healed with simple soothing remedies. This percentage was higher in the practice of pediatricians and was about 50% in that of general practitioners. The principal causes of the dermatitis were contacts with alkalies and external medications.

The season of onset of dermatitis in infants up to 2 years of age was shown in an analysis of the records of 500 such infants. Of these, 75% had their onset in the seven cold months (September-March), with an average of 10% a month. We believe these figures have significance, at least to persons living in the north temperate zone, where doors and windows are closed in September and the heat turned on and the process reversed late in April or early in May. There must be some explanation for the fact that dermatitis develops in twice as many infants a month in cold months as in warm months. For many reasons we have concluded that this increased incidence is due primarily to exposure to wool, both by contact and by inhalation, during the cold months and its relative absence during the warm months. This factor will be discussed later.

The time of onset of atopic dermatitis in a group of children from 5 to 10 years of age was determined by an analysis of 300 records. Thirty-two per cent had their onset in the seven cold months (September-March), with an average of 11.7% a month; 18% had their onset in the five warm months (April-August), with an average of 3.6% a month. The discrepancy between these figures and those for the

From the University of Buffalo School of Medicine, Department of Dermatology and Syphilology.

Presidential address read at the meeting of the American Dermatological Association, Lake Placid, N. Y., June 9, 1953.

younger age group can be explained by the amount of exposure to, and the degree of natural protection against, wool fiber. Among the factors of difference, it must be remembered that the horny layer of older children gives more protection against fibers than does the horny layer of young infants. Generally speaking, older children are out in the air more and are exposed to less wool in the form of clothing than are infants.

In a group of 98 infants 2 years of age and under with atopic dermatitis, examined five years or more later, 79, or approximately 80%, continued to have chronic atopic dermatitis and 19, or, approximately 20%, were free of dermatitis at the time of examination.

Of 300 patients 2 to 5 years of age with atopic dermatitis, 224, or approximately 75%, were much improved or entirely free of dermatitis during the summer months and 76, or approximately 25%, had dermatitis as severe in the summer as in the winter. Only two patients were entirely free of dermatitis in the winter.

Of 89 patients with chronic atopic dermatitis followed for 5 to 26 years, 6 were followed for 20 years, 6 for 15 years, 17 for 10 years, and 59 for 5 years. For 59 of the entire group, or approximately two-thirds of the patients, wool was shown to be the dominant allergenic factor, both by tests and by clinical experience. In 26 cases, pollens were an important allergenic factor in addition to wool and other allergens. In only three cases were foods incriminated, and never as the sole allergenic factor.

Of 100 patients between the ages of 2 and 10 with chronic atopic dermatitis, 28% gave a history of clearing for from one to five years.

Combining the figures of 28% for temporary remission and 10 to 20% for spontaneous cure gives a figure of 38 to 48%. This figure must always be borne in mind in evaluating the results of treatment in infants and young children with atopic dermatitis.

Of 31 patients with atopic dermatitis who were followed for more than 10 years, asthma developed in 13, or approximately 40%. Of 176 patients with atopic dermatitis first seen at age 15 or over, 121, or nearly 70%, had symptoms of asthma at the time of first examination. These figures would suggest some apparent effect from a partial reduction in the exposure to wool, feathers, and so on by our treatment regimen.

Of 76 patients who followed our advice and went to southern Florida, 66, or almost 90%, reported satisfactory clearing while in the south, with recurrence when they returned north during the cold months. There were two patients whose dermatitis cleared promptly while they were in the south but failed to clear on subsequent visits.

From a practical standpoint our patients from the north have done better in Key West or in the Miami area than in northern Florida or Arizona. This has been true whether the patient has been accompanied by one or both parents, husband or wife, nurse, or friend or has been alone. It is the common experience of dermatologists to be consulted by patients with atopic dermatitis of one or many years' duration who have had complete and often repeated allergy studies and many forms of treatment without significant results. When there is a history of a summer remission and a winter recurrence, it has become our practice to urge that a minimum of three weeks be spent during the winter in southern Florida. When such a visit is impossible, we urge hospitalization in a relatively allergen-free room.

"Allergen-free" implies no admittance to the room of friends or relatives and admittance only of physicians and nurses in uniform. When such conditions have been met and only soothing treatment applied, at least 90% of the patients have improved satisfactorily. Improvement occurs under allergen-free conditions whether the climate of the environment is warm and dry, warm and moist, or at a temperature of 70 to 72 F. and the air either dry or moist. Although we recognize that in all cases of atopic dermatitis there is a disturbed sweat mechanism, it has been our observation that this makes little but temporary disturbance in the healing period if allergenic contactants and inhalants are removed. We are convinced that wool is the dominant allergen, although there are other minor and major factors, such as specific hypersensitivity to fungi, Lycopodium, products of bacterial growth, and foods, and psychogenic disturbances. If a patient with atopic dermatitis has a history of routine clearing in the summer and recurrence each winter or clearing in the south during the winter or in a hospital room, the burden of proof must be upon the physician to show that wool, as a contactant and inhalant, is not a major factor in the production of the disease. Along this line, it is well to call attention to the fact that authorities have stated for many years that approximately 95% of persons with atopic dermatitis have positive intradermal tests to house dust and at least 90% to wool protein.

From 1929 to 1938,[1] we tried to eliminate wool both as a contactant and as an inhalant. In spite of personal inspection of the environment, we were never sure that our admonition to eliminate wool was effective. We began to examine samples of house dust microscopically and to estimate the percentage of wool fiber in house dust in the air. Samples of dust accumulated for a few days on book shelves, table tops, and piano tops were examined in water suspension and the percentage of wool fibers estimated. With a little experience it became easy to count 100 fibers and thereby arrive at an index of the amount of wool in the air of the room in which the dust was collected. Several modifications of this method were tried, especially in the collecting of the house dust on glass plates covered with a film, but there was no demonstrable superiority over the original method. We realized that the method was only a rough scientific determination, but it still gave us the information we were seeking; namely, an answer to the question, Does the admonition to eliminate all wool really have any significance? The answer to this question was immediately found to be No. Without the complete removal of all woolen rugs, carpets, and blankets from the entire house or apartment, the advice to eliminate wool was found to be of no significance. From 1938 to 1952 this rough method was used with a great deal of satisfaction, but in the latter year Millon's reagent [2] was used as a stain, and it has proved eminently satisfactory.

METHOD OF DUST ANALYSIS

The patient or parent is instructed to select an area of 2 to 3 sq. ft., such as a table top, mantel, book shelf, or piano top, where dust settles freely from the air. Dust is allowed to settle on this area for four to seven days. It is then scooped into an envelope with the side of the hand or a flat stick, such as a ruler. The envelope is labeled and mailed or brought to the office.

1. Osborne, E. D., and Walker, H. L.: Contact and Environmental Allergens as a Cause of Eczema in Infants and Children, Arch. Dermat. & Syph., **38**:511-525 (Oct.) 1938.

2. Matthew's Textile Fibres, Ed. 5, New York, John Wiley & Sons, Inc., 1947.

The dust sample on receipt usually consists of a variety of fibers matted together, plus a small amount of amorphous particles of dirt.

A small portion of the dust is placed on a glass slide. The fibers are teased apart, and a drop of Millon's reagent is added. A cover slip is placed over the preparation. The slide may be gently heated to hasten staining.

Millon's reagent is prepared by dissolving 1 cc. of mercury in 9 cc. of 94% nitric acid and then adding 10 cc. of water. The addition of a few crystals of a wetting agent, such as sodium arylsulfonate or lauryl sulfoacetate, reduces air bubbles and speeds staining.

The slide is then examined microscopically under low power. Hairs, man-made protein fibers, and silks stain from light orange to reddish brown. Wool fibers are readily distinguished from the fibers of cotton, nylon, rayon, and other synthetics by the latter fibers' failure to stain. Wool fibers are readily distinguished from silk fibers by their numerous cuticular scales, or overlapping cells, the margins of which are visible as irregular cross striations, not seen in other types of fibers. To differentiate wool from other animal hairs, special tests may be used. From a practical standpoint, this differentiation is not necessary. One hundred fibers are counted. Four or five portions of a dust sample are usually examined and the average wool percentage determined. If Millon's reagent is not available, the dust may be mounted in glycerin or water and the wool fibers identified under high power by their microscopic characteristics.

Microscopic examination of house dust samples has yielded us the following information.

In the average house or apartment in the Buffalo area, the amount of wool fiber in the house dust ranges from 5 to 10% as the minimum and up to as high as 50% during the seven cold months. During the five warm months the amount of wool fiber in the average home or apartment will drop to 1 or 2% in most cases, with a maximum of about 5%.

Modern schools with filtered air and lockers for the children's outer garments generally show less than 1% wool content in the dust.

The usual admonition to eliminate wool has little effect upon the percentage of wool fiber in the house dust unless all woolen rugs, carpets, and blankets and fuzzy woolen clothing are removed.

Removal of all woolen rugs, carpets, and blankets and fuzzy woolen clothing reduces the amount of wool fiber in the house dust to less than 2%, and often less than 1%.

The skin of most persons with atopic dermatitis which clears or markedly improves during the warm months or in southern Florida during the cold months begins to itch and burn when the amount of wool fiber in the house dust exceeds 2%.

The highest concentrations of wool fiber are found in the dust collected nearest the floor. When playing, studying, or watching television on the floor, children will inhale appreciably more wool dust than they do when sitting on chairs.

The best protection against wool fiber in house dust is afforded by the complete elimination of woolen rugs, carpets, and blankets and fuzzy woolen clothing and the installation of an electric filtering device. Air filters in windows in individual rooms, although beneficial, do not prove completely satisfactory unless wool in other parts of the house has been completely removed.

In the Buffalo area, within a few days after doors and windows have been closed and the heat turned on, the percentage of wool fiber in the house dust begins to mount rapidly. As soon as the doors and windows are open and the heat turned off in the spring, the process is reversed. The presence or absence of moisture in the air is obviously of great importance to the ability of wool fiber to float in the air.

To persons with atopic dermatitis for whom wool is the dominant allergen, the visiting of friends', neighbors', or relatives' homes where wool has not been eliminated has proved a definite hazard. Sufficient wool fiber may be inhaled in a few minutes to produce a severe exacerbation which lasts several days or weeks.

In the Buffalo area, and presumably in all areas in the north temperate zone, there are periods of cool weather during the summer, when the doors and windows are closed and the heat is turned on. During these periods the content of wool fiber in the house dust may rise sufficiently to produce an exacerbation in susceptible persons.

In 1938, Osborne and Walker [1] reported examples of atopic dermatitis induced by both local contact with and inhalation of wool. Tuft [3] reported similar cases. More recently Hill [4] reported cases of atopic dermatitis due to local contact with wool and, it would appear from perusal of his reported cases, due to inhalation of wool fiber. From our observations we have concluded that wool is the dominant allergenic factor in approximately two-thirds of the cases in which atopic dermatitis becomes exacerbated during the cold months and clears during the warm months of the year. Local contact with wool fiber is a frequent cause of the localized contact-type of papular dermatitis at the points of contact with woolen clothing, such as woolen hoods, caps, collars, coats, mufflers, sweaters, and mittens, and with woolen rugs, carpets, blankets, and furniture coverings. The areas of contact are principally the cheeks, neck under the chin, sides of the neck, wrists, and hands. If exposure to wool is maintained and inhalation of wool fiber continues, in a high percentage of cases there develops a generalized hypersensitivity to wool protein, which is manifested by the characteristic flexural dermatitis of children and adults.

REPORT OF CASES

CASE 1.—A girl aged 2 years 4 months was followed six and one-half years.

History.—Her paternal grandfather had hay fever. She was adopted at the age of 5½ months. Soon thereafter a diaper rash appeared and was followed by a generalized exfoliative dermatitis, which healed in two or three months. Onset of a flexural dermatitis occurred at age 9 months. She had an attack of hives at 1 year of age, which was presumed to be due to wheat or peanut butter. At 20 months of age there developed a contact type of dry dermatitis, said to be due to a wool sweater. This slowly developed into a generalized eruption. She was hospitalized for two weeks in one hospital, where she was treated with local applications, and in another hospital for four weeks, with a moderate degree of improvement. As soon as she was returned home there was a severe recurrence. During her hospitalization skin tests were done, and many positive reactions were secured, including reactions to fruits, wheat, eggs, and wool. Treatment by competent dermatologists yielded no satisfactory results.

3. Tuft, L.: Importance of Inhalant Allergens in Atopic Dermatitis, J. Invest. Dermat. **12**:211-219 (April) 1949.

4. Hill, L. W.: Wool as a Cause of Eczema in Children, New England J. Med. **245**:407-409 (Sept. 13) 1951.

Examination of the patient showed a well-developed, well-nourished, irritable 2-year-old girl. She presented a generalized, dry erythematosquamous dermatitis, more marked on the flexures. There were large inguinal and axillary lymph nodes. Our clinical diagnosis was severe atopic dermatitis.

Course.—The patient was placed in a relatively allergen-free room. Only nurses and physicians in cotton uniforms or gowns were admitted to the room. Colloid baths, 5% boric acid ointment, and calamine lotion were used locally. Rhinitis and bronchitis developed, and then, bilateral middle ear abscesses, which were drained. Within a week after she entered the hospital there began a slow but steady improvement in the skin. There were no restrictions on the diet. Microscopic examinations of dust from the hospital room showed approximately 2 to 3% wool fiber. Because of an upper respiratory infection and bilateral middle ear infections, the parents were advised to take the child to Key West, Fla. She was taken to her home in Pennsylvania and within twenty-four hours suffered a severe exacerbation of her dermatitis. A house dust sample at this time, in spite of removal of all woolen rugs, carpets, and blankets, showed approximately 5% wool fiber. The patient was taken to Key West for a period of three months, from the last of November to the first of March. During this period the skin improved approximately 80%.

At home, the house dust continued to show more than 5% wool fiber in spite of the installation of an electric filtering device. It was finally discovered that one-half of the return flow of air was coming from another apartment in the building. When proper corrections were made and the intake of air was from the outdoors, the percentage of wool fiber in the house dust promptly dropped to less than 1%. For four years, repeated examinations have shown it to be at zero. All woolen rugs, carpets, and blankets were removed. Woolen upholstery was covered, and members of the household have worn only hard-finished clothing. No friends or relatives wearing soft or fuzzy woolen clothing have been allowed in the house. The patient is now, and has been for more than two and one-half years, completely free of dermatitis. Hives still develop from eggs, wheat, chocolate, and pork. She is able to go to school, where there is a modern heating plant with filtered air. Up to this time she has not been allowed to enter any home of her friends or neighbors. Examination of her skin in May, 1953, showed no evidence of an atopic dermatitis, and there was a normal response of her entire skin surface to scratch. This response had likewise been normal two years previously. Exposures to ordinary house dust during the winter months produce an immediate generalized itching and burning. Wearing a woolen mitten or glove for 15 to 30 minutes produces the same result.

CASE 2.—A girl aged 5 years was followed one year.

History.—A dermatitis appeared during the winter, while she was 2 years of age. This was localized on the flexures of the neck, arms, and legs and on the cheeks. A complete series of allergy tests were performed and directions carried out, without significant results. Test diets brought no relief. The dermatitis cleared twice during the summer months and recurred each fall and winter.

Examination.—The patient presented a moderately severe, dry erythematosquamous dermatitis with marked excoriations involving the cheeks, the sides of the neck, the neck under the chin, the flexures of the arms and legs, and the wrists. A dust sample from the living room showed approximately 55% wool fiber.

Course.—All woolen rugs and carpets were removed. Woolen blankets were placed inside blanket covers. Feather pillows were replaced with foam rubber pillows. All soaps and laundry chemicals were removed from the child's environment. Two months after treatment was started, a dust sample from the living room showed less than 1% wool fiber. The child's skin has remained free of dermatitis for slightly more than one year, including an entire winter.

CASE 3.—A woman aged 41 was followed 9 years.

History.—This adult patient gave a history of a flexural eczema from infancy. She had been free of dermatitis from about the age of 4 to the age of 8 years. She had never been free of dermatitis since that time. She routinely improved or became entirely free of dermatitis during the summer months and suffered an exacerbation in September or October. She had been under the care of many allergists and dermatologists, with repeated tests, desensitization treatment, and test diets, without satisfactory results. During a period of hospitalization for

three weeks during the winter when she was 30 years of age, the dermatitis markedly improved. She had received large amounts of x-ray therapy over a period of at least 10 years. Because of her nervous condition she had submitted to extremely competent psychiatric examination and treatment, without results.

Examination.—The patient was an apparently healthy, high-strung, nervous, middle-aged woman, brought in by her husband against her will. She presented a moderately severe dry erythematosquamous dermatitis over the face, the neck, the flexures of the arms, and the popliteal areas. Her skin was markedly thickened and hyperpigmented. There was a diffuse radiodermatitis over the face, neck, and chest.

Course.—Cooperation on the part of the patient was not easy to obtain. In spite of financial embarrassment, the husband was persuaded to take his wife to Key West, Fla., where, in a period of less than three weeks, her skin improved more than 80%. Her entire personality and outlook on life changed. While the patient was in the south the home was investigated. The house dust in the living room and the patient's bedroom showed more than 40% wool fiber. The house was completely renovated. All woolen rugs, carpets, and blankets and feather pillows were removed. A room was built in the basement, which was entered from an outside door and served as an air lock. The husband and two sons regularly changed into cotton clothing when entering the house. An additional room for the patient was built onto the rear of the house adjoining the kitchen. When the patient returned home, in March, the percentage of wool fiber in the house dust in the living room and in her bedroom was less than 1%. The patient rarely entered any other part of the house except her own room and the kitchen, where she met other members of her family. For a period of more than eight years she has remained almost totally free of atopic dermatitis except at times in the winter, when she meets with her friends and neighbors at a party or church function or visits her relatives. Her reaction to scratch in April, 1953, was normal. The wearing of a woolen glove or mitten induced, within a few minutes, a violent burning and itching of the entire skin surface.

OBSERVATIONS ON DERMOGRAPHISM, VASOCONSTRICTION AND THE X-FACTOR

Recent literature has emphasized the occurrence of white dermographism in atopic dermatitis, a phenomenon that has been known for many years. The studies of Eyster, Roth, and Kierland [5] have emphasized the vasoconstriction occurring in atopic dermatitis, as well as increased vascular activity. It is interesting to note from their studies that when the dermatitis was active, the season had little effect on the vasoconstriction and on vascular activity. These studies confirm the impression that in atopic dermatitis, during the active stage, vasoconstriction and vascular instability are present. The studies also explain the physiopathologic background for white dermographism and indicate that the overreaction of the nervous, respiratory, gastrointestinal, and vascular systems may be due to the agent that produces white dermographism in the skin.

Sulzberger and Baer [6] have recently editorialized, in reviewing the paper by Hill,[7] as follows:

> We are of the opinion that atopic dermatitis is not primarily an allergic disease. This does not deny the fact that allergenic factors play a role in some cases of the disease. However, the major agency is what Hill refers to as the X-Factor. There are quite a number of abnormal features, more commonly found in atopic dermatitis than in any other dermatoses, and

5. Eyster, W. H.; Roth, G. M., and Kierland, R. R.: Studies on Peripheral Vascular Physiology of Patients with Atopic Dermatitis, J. Invest. Dermat. **18**:37-46 (Jan.) 1952.

6. Sulzberger, M. B., and Baer, R. L.: The 1952 Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1953, p. 135.

7. Hill, L. W.: Nomenclature, Classification and Pathogenesis of 'Eczema' in Infancy, A. M. A. Arch. Dermat. & Syph. **66**:212-222 (Aug.) 1952.

common among them is the increased tendency to vasoconstriction. This is easily demonstrated by elicitation of white dermographism, and may be related to a cardinal local factor (or Hill's X-Factor) in atopic dermatitis.

We have made many observations along this line in clinical cases which may be of importance. Patients with a localized contact type of dermatitis due to wool will show a white dermographism in most instances in the area of eruption. Other areas of the skin will give a normal red reaction to scratch. Within a period of a few months after the localized contact type of wool dermatitis has disappeared, if there has been no inhalation of wool fiber, the previously involved localized areas will give a normal red response to scratch. In cases in which extensive generalized dermatitis goes into a remission for two or three months during the summer or after complete removal of wool for a period of two or three years, the tendency to vasoconstriction disappears and the skin returns to a normal response to scratch. In view of these observations, it has seemed to us that Hill's so-called X-factor resides in the nature of the allergen producing the specific hypersensitivity. A logical conclusion would therefore be that it is the nature of the protein molecule of wool and other related substances that is responsible for the characteristic vasoconstriction, and not the usual vasodilatation, with red dermographism, seen in response to other types of protein molecules. If vasoconstriction is the characteristic response to wool protein molecules, this could well explain all the other stress manifestations noted in the nervous, respiratory, gastrointestinal, and vascular systems, as well as the induction of abnormal immunologic, endocrine, sweat, and other reactions seen in the atopic person. It is known that certain break-down products of proteins produce vasodilatation, as in the case of histamine. Likewise, other products derived from the protein molecule produce vasoconstriction, such as parahydroxyphenylethylamine (Tyramine) and epinephrine. Certainly, research is indicated along this line. Finally, it is our belief that the mechanism in atopic dermatitis lies in the nature of the protein molecule producing the hypersensitivity and that it is not a factor inherent in the individual.

SUMMARY

There have been presented pertinent data regarding the natural course of treated and untreated atopic dermatitis. Approximately three-fourths of the patients undergo summer remission and winter recurrence. We believe that in at least two-thirds of these wool is the dominant, although not always the only, allergen. When atopic dermatitis clears in the summer and recurs in the winter, the burden of proof is on the physician to show that wool is not a factor. The usual admonition by physicians to eliminate wool and house dust brings no satisfactory results. Microscopic examination of house dust samples is of great value in checking the presence of wool fiber. Finally, it is our belief that further investigation will show that the nature of the protein molecule is responsible for the type of cutaneous response, as well as for disturbances in the nervous, gastrointestinal, and cardiovascular systems that are commonly seen in patients with atopic dermatitis.

ASTEROL TREATMENT OF SUPERFICIAL DERMATOMYCOSES DUE TO T. MENTAGROPHYTES AND T. PURPUREUM

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IN TWO previous papers [1] we have reported our experience with Asterol dihydrochloride (2-dimethylamino-6-[beta-diethylaminoethoxy] benzothiazole) in tinea capitis due to Microsporum audouini. One of these communications [1b] also describes our results with this antifungal agent in cases of moniliasis and of tinea versicolor.

We have since studied the effectiveness of Asterol dihydrochloride in superficial mycological infections due to Trichophyton mentagrophytes and Trichophyton rubrum (purpureum), and our findings are herewith reported.

DERMATOMYCOSES DUE TO T. MENTAGROPHYTES

Thirty-nine patients with superficial fungus infections were studied, in all of whom T. mentagrophytes was culturally determined as the causative organism. As is shown in Table 1, listing the distribution of the areas of involvement and the results obtained, about two-thirds of these patients had infections in the acute phase and one-third in the chronic phase.

The patients with acute infections were first treated, depending on the area of involvement, with foot baths or wet dressings of boric acid or aluminum acetate (Burow's) solution (1:30). When the acute and pyodermic phases had completely subsided asterol tincture was used during the day and asterol ointment at night. After evaporation of the former, Asterol dusting powder was administered to the lesions. A foot bath or compresses preceded the application of Asterol ointment. Patients with tinea pedis sprinkled Asterol dihydrochloride dusting powder into socks and shoes.

The treatment plan for the patients with chronic infections was essentially the same, but, of course, in only rare cases were measures required to combat acute phases of the lesions.

None of the four patients with groin involvement used the alcoholic solution. They applied Asterol ointment at night and Asterol dusting powder during the day.

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The Asterol preparations used in this study were supplied by Hoffmann-La Roche Inc., Nutley, N. J., through the cooperation of Dr. Leo A. Pirk.

1. (*a*) Edelson, E.; Craster, C., and Haskin, A.: Evaluation of a New Drug for Topical Therapy of Tinea Capitis, A. M. A. Arch. Dermat. & Syph. **64**:444-448 (Oct.) 1951. (*b*) Edelson, E., and Haskin, A.: Treatment of Superficial Mycological Infections with a New Antifungal Agent, ibid. **66**:244-250 (Aug. 1952).

Patients were pronounced cured if a clinical cure was corroborated by negative cultural findings and if they remained well for at least two weeks—the period of follow-up observation. Patients were listed as considerably improved if there was marked clinical improvement (often even cultural negativity) with the persistence of some residual clinical symptoms, such as, for instance, scaliness.

By these criteria, 22 of the 39 patients studied were considered cured and 10 were considered much improved.

TABLE 1.—*Distribution of Acute and Chronic Infections in Thirty-Nine Patients with T. Mentagrophytes Infections Treated with 5% Asterol Dihydrochloride and Summary of Results*

		Acute Infections				Chronic Infections			
Area of Involvement	Total No. of Patients	No. of Patients	No. Cured	No. Considerably Improved	No. Unimproved	No. of Patients	No. Cured	No. Considerably Improved	No. Unimproved
Feet	31	22	13	5	4	9	5	2	2
Hands	3	2	1	1	..	1	..	1	..
Groins	4	2	1	..	1	2	1	1	..
Flank (right)	1	1	1	..	..	..	..	..	..
Totals	39	27	16	6	5	12	6	4	2

TABLE 2.—*Fifty-Eight Patients with T. Rubrum Infections Treated with 5% Asterol Dihydrochloride and Summary of Results*

Area of Involvement	No. of Patients	No. Cured	No. Considerably Improved	No. Unimproved
Nails				
Toes	21	4	..	17
Fingers	6	1	..	5
Skin				
Feet	23	5	6	12
Lower abdomen, mons pubis, groins, genitals, and flanks (either alone or multiple sites)	8	4	1	3
Totals	58	14	7	37

The average duration of treatment of the cured patients in the individual groups ranged from 17 to 29 days; of the considerably improved patients, from 18 to 36 days, and of the unimproved patients, from 19 to 25 days.

We employed Asterol dihydrochloride also in treatment of 23 additional patients with very similar lesions with approximately the same results. However, these patients are not included in this study because we were unable to obtain positive cultures in these instances.

DERMATOMYCOSES DUE TO T. PURPUREUM (RUBRUM)

Fifty-eight chronic cases were studied over a period of two years. In all these instances T. rubrum was culturally determined as the offending organism. As is shown in Table 2, listing the distribution of the areas of involvement and the results obtained, there were 27 patients with onychomycosis (average number of involved nails was three), 23 with infections of the feet, and 8 with infections of the glabrous skin.

In the cases with nail involvement, the nail plates were sanded with emery boards at frequent intervals by the patients at home. In some instances, sanding with an electric chiropodic drill and débridement were performed in the clinic. Asterol ointment was applied to the infected nails every night with a small brush.

For patients with involvement of the feet or the glabrous skin, Asterol tincture was used in the morning followed by sprinkling Asterol dusting powder on the lesions. The ointment was applied every night. Again, patients with tinea cruris did not use the tincture in the groins, but employed Asterol ointment at night and Asterol dusting powder during the day.

Patients with onychomycosis were considered cured when their involved nails assumed the appearance of noninfected nails. In this group, results were classified either as cures or as failures; thus, patients showing moderate improvement, as might be manifested by decreased irregularities of nail configuration, were grouped together with the unimproved patients.

Patients with infections of the feet or glabrous skin were considered cured when the lesions had cleared and when cultural findings were negative. In some instances, we observed a residual pigmentation which, however, subsided subsequently without therapy. All cured patients remained clinically well for two weeks—the period of follow-up observation.

As is shown in Table 2, of the 27 patients on onychomycosis 5 were cured. The period of treatment ranged from 32 to 40 weeks. The patients with nail involvement classified as unimproved were treated for a minimum of 24 and a maximum of 30 weeks. It appears also from Table 2 that 9 of the 31 patients with infections of the feet or glabrous skin were cured. In these instances, the period of treatment ranged from 21 to 29 days. The seven patients classified as markedly improved were those with multiple lesions of which at least one responded very satisfactorily, while the other lesions remained unimproved. The duration of treatment in the latter instances ranged from 22 to 35 days. The average time of treatment of the unimproved patients with skin lesions was 33 days.

COMMENT

The above results with Asterol in treatment of T. mentagrophytes and T. rubrum infections are not so striking as those we observed with this drug in tinea capitis due to M. audouini,[1] in moniliasis,[1b] and in tinea versicolor.[1b] However, it must not be expected that a given antifungal agent which is particularly effective in combating one or several organisms will be productive of equally good results in the treatment of lesions caused by dermatophytes of a different genus or by different species of the same genus.

Our criteria for cure of the T. mentagrophytes infections included cultural negativity. Since most workers consider as cured patients who are clinically well, without studying postmedication cultures, we feel that the cure rate recorded in this report has particular significance.

It is very difficult to determine the comparative merits of various agents recommended for the treatment of dermatomycoses. In fact, it would be possible to weigh the effectiveness of one preparation against another objectively only by using the method of paired symmetrical comparison.[2] Not only would this be a very cumber-

2. Sulzberger, M. B., and Kanof, A.: Comparative Evaluation of Preparations for Prophylaxis and Treatment of Fungus Infections of the Feet, U. S. Nav. M. Bull. **46**:822-833 (June) 1946.

some procedure, but the numbers of patients available with bilateral symmetrical lesions, which would lend themselves for this kind of evaluation, would be too small to yield significant results. Therefore, in assessing the comparative virtues of antifungal drugs, one has to rely partially on clinical impressions rather than wholly on objective findings. From the results reported here, we would agree with Stritzler and associates [3] that fungus infections due to T. mentagrophytes respond at least as well to Asterol dihydrochloride as to the undecylenic acid preparations. As for T. rubrum infections, results with Asterol are about equal to those obtained with other agents.

It appears from Table 3 that the cure rates in our series and in those reported by Stritzler and collaborators,[3] on the one hand, and by Ravits,[4] on the other, are in fair agreement. This table takes into account only patients with infections of

TABLE 3.—*Cure Rates with 5% Asterol Dihydrochloride Reported by Three Clinical Students in Fungus Infections of the Feet and Glabrous Skin Due to T. Mentagrophytes and T. Purpureum*

Student	T. Mentagrophytes			T. Rubrum		
	No. of Patients	No. Cured	Cure Rate, %	No. of Patients	No. Cured	Cure Rate, %
Edelson	39	22	56.6	31	9	29
Stritzler [3]	41	22	53.7	45	17	37.7
Ravits [4]	18	11	61	5	2	..

the feet and the glabrous skin because Stritzler in his series reported no patients with onychomycosis due to T. mentagrophytes or T. rubrum.

SUMMARY

A study of 97 cases of mycoses of the feet, glabrous skin, and nails is presented. In 39 of these, Trichophyton mentagrophytes and in 58, Trichophyton rubrum were culturally determined as the offending organisms. In the former group, two-thirds of the cases were of the acute and one-third of the chronic variety. All T. rubrum infections were of long standing. The application of Asterol dihydrochloride ointment, tincture, and dusting powder was attended by gratifying results in infections due to T. mentagrophytes. In T. rubrum infections the cure rate was not higher than with other antifungal preparations. Generally, the cure rate produced by Asterol in trichophyton infections was not so high as it was in Microsporum audouini infections, moniliasis, and tinea versicolor. Our results are shown to be in fair agreement with those reported by other investigators.

3. Stritzler, C.; Fishman, I. M., and Laurens, S.: Treatment of Superficial Fungus Infections with a New Antifungal Agent, Tr. New York Acad. Sc. **13**:31-37 (Nov.) 1950.

4. Ravits, H. G.: Treatment of Superficial Dermatomycoses with Asterol® Dihydrochloride, J. A. M. A. **148**:1005-1007 (March 22) 1952.

NEOMYCIN LOTION IN TREATMENT OF CUTANEOUS BACTERIAL INFECTIONS

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DURING the time that has elapsed since Waksman [1] and his co-workers discovered neomycin, it has become one of the accepted antibiotics for the treatment of cutaneous bacterial infections. Numerous investigators [2] have reported that this antibiotic is a very valuable therapeutic agent for the topical treatment of bacterial infections of the skin when applied either as an ointment or in aqueous solution. The work of Livingood [3] and his co-workers indicates that it is particularly effective for staphylococcic infections and that its spectrum includes a fair percentage of most of the bacteria which are of importance in the etiology of cutaneous bacterial infections.

Perhaps it is appropriate to state that there is no one antibiotic [4] for topical treatment of skin infections that is distinctly superior to all others. For example, it is generally agreed that both oxytetracycline (Terramycin) and chlortetracycline (aureomycin) are superior to neomycin in the treatment of infections due to hemo-

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The neomycin used in this study was supplied by The Upjohn Company, Kalamazoo, Mich.

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1. Waksman, S. A., and Lechevalier, H. A.: Neomycin, a New Antibiotic Active Against Streptomycin-Resistant Bacteria, Including Tuberculosis Organisms, Science **109**:305-307 (March 15) 1949.

2. (*a*) Livingood, C. S.: Pyogenic Cutaneous Infections in Children: Their Modern Management, Texas J. Med. **47**:469-474 (July) 1951. (*b*) Herrell, W. E.: Current Trends in Antibiotic Therapy, J. Iowa M. Soc. **42**:287-292 (July) 1952. (*c*) Forbes, M. A., Jr.: A Clinical Evaluation of Neomycin in Different Bases, South. M. J. **45**:235-239 (March) 1952. (*d*) Falk, M. S., and Allende, M. F.: The Use of Neomycin in Dermatology: Preliminary Report, Permanente Found. M. Bull. **9**:75-80 (July) 1951. (*e*) Kimberly, L. W.: The Treatment of Pyogenic Skin Infections with Topical Neomycin, J. Iowa M. Soc. **42**:221-222 (May) 1952. (*f*) Kile, R. L.; Welsh, A. L., and McAfee, G. D.: Topical Use of Neomycin: Preliminary Reports, Arch. Dermat. & Syph. **62**:911 (Dec.) 1950. (*g*) Kile, R. L.; Rockwell, E. M., and Schwartz, J.: Use of Neomycin in Dermatology, J. A. M. A. **148**:339-343 (Feb. 2) 1952.

3. Livingood, C. S.; Nilasena, S.; King, W. C.: Stevenson, R. A., and Mullins, J. F.: Pyogenic Infections Treated with Neomycin, J. A. M. A. **148**:334-339 (Feb. 2) 1952.

4. (*a*) Livingood, C. S., and Mullins, J. F.: Management of Bacterial Infections of the Skin, Postgrad. Med. **12**:15-26 (July) 1952. (*b*) Kadison, E. R.; Volini, I. F.; Hoffman, S. J., and Felsenfeld, O.: Neomycin Therapy: Its Use in Virus Pneumonia, Tuberculosis and Diseases Caused by Gram-Negative Bacteria, J. A. M. A. **145**:1307-1312 (April 28) 1951. (*c*) Rattner, H., and Rodin, H. H.: Treatment of Pyodermas with Penicillin 92: Comparison with Neomycin and Bacitracin, A. M. A. Arch. Dermat. & Syph. **65**:656-662 (June) 1952.

lytic streptococci but not quite as effective in staphylococcic infections.[4a] Also, polymyxin B is superior to neomycin for Pseudomonas infections. The advantages and disadvantages of the available antibiotics for the local and systemic treatment of bacterial infections of the skin have been summarized by Livingood and Mullins.[4a] Neomycin is not used systemically because of its ototoxic and nephrotoxic effects.[4b] Therefore, possible sensitization to the antibiotic after topical treatment does not deprive the patient of a valuable therapeutic agent for the treatment of a subsequent systemic infection as may be the case with oxytetracycline, chlortetracycline, and penicillin.[5] It has been reported[4a] that the absorption of neomycin after topical application is extremely low and of no significance unless it is applied to large denuded areas for prolonged periods of time. However, this possible absorption factor should not be ignored if the patient has extensive involvement and if treatment is continued for more than six to eight days.

In certain patients, it is quite obvious that there is a distinct advantage in using a lotion rather than wet dressings or an ointment. For example, in the treatment of a patient with extensive involvement, the use of a lotion is more economical and is easier and nicer to use. Neomycin is the only broad-spectrum antibiotic available to date which is stable in an aqueous solution for an indefinite period. For this reason, it is possible to prepare lotions which are stable indefinitely.

TABLE 1.—*Bacteriologic Studies*

Causative Organism	Cases, No.	Sensitivity to Neomycin in γ					Sensitivity Tests Done, No.
		0-1	5 or Less	10 or Less	25 or Less	50 or Less	Over 50	
Hemolytic Staphylococcus	95	26	24	9	2	0	8	69
Nonhemolytic Staphylococcus	4	1	0	0	0	0	0	1
Beta-hemolytic Streptococcus	9	3	3	1	0	1	0	8
Proteus	4	0	0	0	0	0	0	0
Pseudomonas	4	0	0	0	0	1	0	1
Sarcina lutea	1	0	0	0	0	0	1	1

MATERIALS AND METHOD OF APPLICATION

Various combinations were tried and the following are the ingredients of the preparation used in this study: 6 mg. neomycin sulfate (flushed 20%), methylparaben U. S. P., butyl parahydroxybenzoate, a glyceryl monostearate preparation (Tegacid Regular [Goldschmidt Chemical Corp.]), propylene glycol U. S. P., polysorbate 80 U. S. P., spermaceti U. S. P., and distilled water to make 120.0 cc.

Cutaneous moniliasis at the site of application has been reported by several investigators[6] as a possible complication of local treatment with the broad-spectrum antibiotics, especially with neomycin. Therefore, it seemed desirable to include a moniliastatic agent. Methylparaben and butyl parahydroxybenzoate are the moniliastatic agents that were used.

The lotion was used in the treatment of 335 patients. Of these, 126 had cutaneous bacterial infections. In the other 209 patients, neomycin lotion was applied to removal sites after electrocoagulation of epitheliomas, keratoses, verrucae, etc. In the latter group, the patient was instructed to apply the lotion to the involved part twice daily. The other 126 patients were instructed to cleanse the areas with soap and water before the application of the lotion. In most instances, the affected areas were not covered with a dressing.

5. Sulzberger, M. B., and Baer, R. L., Editors: The 1950 Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1951, p. 10.

6. Livingood.[2a] Forbes.[2e] Kile.[2g] Livingood.[3]

BACTERIOLOGIC STUDIES

Of the 126 patients with cutaneous bacterial infections, 117 cultures were done. The organisms which were isolated and the results of in vitro multiple tube sensitivity tests are summarized in Table 1.

Hemolytic staphylococci were cultured from approximately 81% of the cutaneous bacterial infections seen in this study. Beta-hemolytic streptococci were cultured from 6%, and from the other infections nonhemolytic staphylococci, Proteus, Pseudomonas, and Sarcina lutea were isolated. It is noted in Table 1 that about 84% of the bacteria were sensitive to 10 γ per cubic centimeter or less of neomycin.

RESULTS

In this series of 126 patients, 109 responded satisfactorily in seven days or less. Of these 109 patients, 62 responded in from two to four days. As summarized in Table 2, there were 14 patients who did not have a favorable therapeutic result within 10 days, and these were considered failures. The infection in seven of these patients cleared after the application of neomycin ointment or neomycin cream. Unfortunately, cultures were obtained on only three of these seven infections which

TABLE 2.—*Results of Treatment with Neomycin*

Diagnosis	Cases, No.	Time, Days			Failures	Reactions
		2-4	5-7	8-10		
Impetigo	50	30	18	0	2	0
Impetiginized eczematous dermatitis	37	17	12	2	6	0
Otitis externa	19	4	11	1	3	0
Folliculitis	12	7	4	0	1	0
Ecthyma	7	4	2	0	1	0
Bacterial paronychia	1	0	0	0	1	0
Total	126	62	47	3	14	0

did not respond favorably. From one patient Pseudomonas was cultured, and from the other two hemolytic staphylococci.

The patients with impetigo, folliculitis, and ecthyma responded more rapidly than those with impetiginized eczematous dermatitis and otitis externa. The cases listed as impetiginized eczematous dermatitis consisted of patients with an underlying condition such as seborrheic dermatitis, atopic eczema, or secondarily infected tinea pedis. Of the 19 patients with otitis externa, many had used other antibiotics prior to the institution of neomycin therapy. The majority of these patients had an underlying seborrheic dermatitis of the external ear canal. The results in these particular patients were comparable to those obtained by Falk and Allende,[24] who used the ointment and an aqueous solution of neomycin.

In this study, no instances of sensitization or primary irritation were seen. Perhaps it is also worth while to mention that there was no irritation of any of the preexisting conditions in the patients with impetiginized eczematous dermatitis. In one patient with impetiginized eczematous dermatitis involving the toes localized cutaneous moniliasis developed. However, five days after the lotion was stopped, a culture was negative for Candida, and the condition had subsided. There was one patient whose condition was irritated by neomycin ointment and another by neomycin cream. In both instances, the medication was stopped and neomycin lotion used. The irritation and infection cleared in both patients.

COMMENT

The results in this series of patients were probably affected in a favorable manner by three factors. First, soap and water was used to cleanse the lesions before the medication was applied. Secondly, this study was conducted with private patients and patients seen in a large University Health Center. Thirdly, 81% of the infections were due to hemolytic staphylococci.

Neomycin, a broad-spectrum antibiotic which is bactericidal in a concentration equal to or only slightly higher than that in which it is bacterostatic,[7] is the only broad-spectrum antibiotic which is soluble and stable in an aqueous solution. Jawetz and Gunnison [8] have divided the antibiotics into two groups based on synergism and antagonism. Neomycin is placed in the first group with penicillin, streptomycin, and bacitracin. Frequently, these were found to be synergistic with each other, occasionally indifferent, but never antagonistic to each other. With that advantage, in addition to the stability of this broad-spectrum antibiotic, it appears that neomycin has a definite place in the treatment of cutaneous bacterial infections.

Tyrothricin,[9] which has as its active principles gramicidin and tyrocidine, is stable only in a water-and-alcohol solution, and for practical purposes it is active only for gram-positive organisms.

Whether or not the mixture of parabens was responsible for the low incidence of moniliasis in this series of patients is questionable. Other factors, such as the location of the lesions, must be considered.

SUMMARY AND CONCLUSIONS

Experience with the topical use of neomycin lotion in the treatment of 126 patients with bacterial infections and on removal sites in 209 patients is reported.

The results indicate that neomycin lotion is an effective agent in the treatment of cutaneous bacterial infections and is of particular value in those due to hemolytic staphylococci.

No sensitization reactions were observed in this series of cases, and the medication was well tolerated even in patients who had a preexisting dermatosis.

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7. Waisbren, B. A., and Spink, W. W.: Comparative Action of Aureomycin, Chloromycetin, Neomycin, Q-19, and Polymyxin B Against Gram Negative Bacilli, Proc. Soc. Exper. Biol. & Med. **74**:35-40 (May) 1950.

8. Jawetz, E., and Gunnison, J. B.: Studies on Antibiotic Synergism and Antagonism: A Scheme of Combined Antibiotic Action, Antibiotics & Chemother. **2**:243-247 (May) 1952.

9. Rammelkamp, C. H.: Use of Tyrothricin in the Treatment of Infections: Clinical Studies, War Med. **2**:830-846 (Sept.) 1942. Lubowe, I. I.: The Use of Bacitracin-Tyrothricin Ointment in the Treatment of Pyogenic Dermatoses, New York J. Med. **51**:611-612 (March 1) 1951. Amorosino, V.: Tyrothricin, in Some Pyogenic Dermatoses, Ann. med. nav. e colon. **55**:481-489 (July-Aug.) 1950. Lehnoff, H. J., Jr.: The Clinical Use of the Newer Antibiotics, Nebraska M. J. **37**:7-9 (Jan.) 1952. Noojin, R. O.: Treatment of the Pyogenic Dermatoses, J. M. A. Alabama **20**:277-283 (Feb.) 1951.

CATHODE RAY TREATMENT FOR LYMPHOMAS INVOLVING THE SKIN

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HIGH-ENERGY cathode rays present an almost ideal form of radiation for the treatment of those lesions involving the skin which can benefit by ionizing energy. Their clinical advantage arises from the possibility of selecting the desired electron penetration by controlling the voltage, from the complete absence of damage to tissue beyond the well-defined electron range, and from the reduced biological effect in the outer layers of radiosensitive skin.

This distribution of cathode ray dose for the treatment of superficial lesions is best obtained by using essentially monoenergetic electrons directed normally into the skin surface.

During the past two years we have treated five patients having lymphomas with extensive involvement of the skin, one patient with inner canthus carcinoma, one with atopic dermatitis, one with sycosis barbae, and three patients presenting keloidal scars. These patients were all treated by delivering to the involved skin area a number of doses of 2,500,000-volt electrons, these electrons being produced by a constant-potential accelerator of the Van de Graaff type and projected into air toward the skin of the patient as a directed stream of particles.

LYMPHOMAS OF THE SKIN

The lymphomas presented challenging cases since they were not, with one exception, amenable to other forms of therapy. Several patients had failed to get relief with superficial x-rays or had reached the stage at which further x-ray therapy could not be tolerated. The lesions presented by five of these patients were so extensive and scattered that any reasonable plan of therapy for relief required almost total surface irradiation. A type of therapy was therefore required which

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would not seriously affect the hematopoietic system and which could be given in such controlled doses as not to inactivate completely the sweat glands, most of which lie in the first 4 mm. of the skin.

The first patient treated with high-energy electrons in this series has now been followed for 18 months. This 69-year-old man with mycosis fungoides, in the infiltrative and tumor stage, was under treatment with conventional x-rays when many new lesions developed and it became impossible to provide further relief. The patient was told of the situation and of the opportunity then being prepared at the Massachusetts Institute of Technology for treating superficial lesions with high-energy electrons. He was extremely pleased to accept this new form of therapy.

The lesions presented by this patient involved nearly all skin areas from the scalp to the tips of the toes, and a plan was evolved which delivered a nearly uniform irradiation of the entire body surface through four basic portals. This was

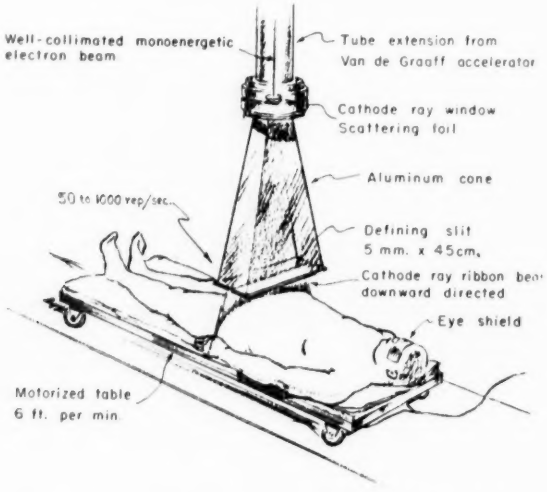
Well-collimated monoenergetic electron beam
Tube extension from Van de Graaff accelerator
Cathode ray window Scattering foil
Aluminum cone
50 to 1000 rep/sec.
Defining slit 5 mm. x 45cm.
Cathode ray ribbon beam downward directed
Eye shield
Motorized table 6 ft. per min.

Fig. 1.—Arrangement for treating extensive superficial malignant lesions with high energy cathode rays.

accomplished, as illustrated in Figure 1, causing the electrons to emerge from the tube into air and then to pass through an elongated slit in an aluminum cone which thus defined a downward directed ribbon of electrons directed toward the patient. The patient, on a motorized bed, was passed through this electron stream, one traverse requiring about one minute and resulting in treatment to the entire upper skin area. Other surfaces were treated by altering the patient's position so as to expose the skin on the anterior, posterior, and two lateral aspects, with supplementary treatments to the crotch and underarm regions.

It was considered important to protect the eyes during treatment. This was done by covering the regions of the eyes with an absorber of low atomic number, or, in other cases in which the eyelids were involved, by using conventional eye cups.

The first patient was treated daily for the first two weeks, three surfaces being treated each time the fist week and two surfaces each time in subsequent treat-

ments—either through two lateral portals or the anterior and posterior portals. The cathode ray dose administered at each visit was 140 rep the first week and 210 rep thereafter, these numbers expressing the dose at the depth of maximum ionization density. After the first two weeks treatment was continued once weekly for eight more weeks and then once every three or four weeks until the present time. Most areas received a total of 2,000 rep in the first 10 weeks, and a few mildly persistent spots have now received 3,500 rep.

Although the patient has received large doses of cathode rays and his entire body surface has been irradiated, he shows no untoward effects 18 months later and remains comfortable. Careful blood studies have not demonstrated any effect

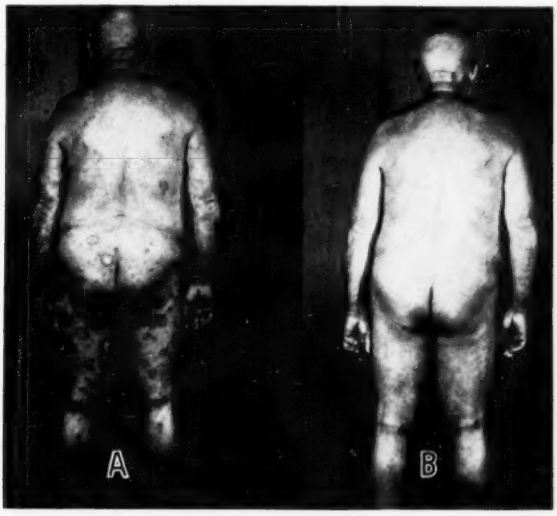

Fig. 2.—Posterior views of the first patient with mycosis fungoides. *A*, five weeks after start of treatment; *B*, 29 days later.

on the hematopoietic system. Figure 2 shows the progressive improvement in the appearance of his skin during the first 10 weeks. This relief has been maintained throughout the period by occasional further electron doses to small areas showing signs of recurrence.

The course of therapy has been changed somewhat in each patient, depending upon the general condition of the patient, the systemic extent of his disease, and upon the length of time he could plan to stay for therapy. All of the patients but one have received symptomatic relief from their skin lesions. The patient failing to receive palliation was a patient with advanced lymphoma and multiple nodes in the axilla and groin. All other patients have shown healing of their lesions, whether of the psoriasiform type or of the infiltrative tumor and ulcerated type. Figures 3 and 4 illustrate the benefit secured from about 2,000 rep administered in a two-week period in two later cases. The one patient whose disease was localized to the forearm has received only one series of treatment and the relief has been satisfactory for

16 months. The other patients are still under observation, six months to one year later, without untoward effects on their skin. In two patients a moderate to severe pancytopenia developed, which we are unable to explain. The condition has been

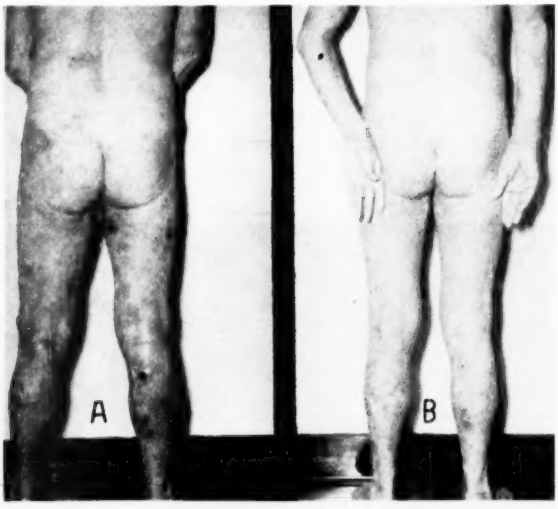

Fig. 3.—Posterior views of the third patient with mycosis fungoides. *A*, at start of treatment; *B*, two months later.

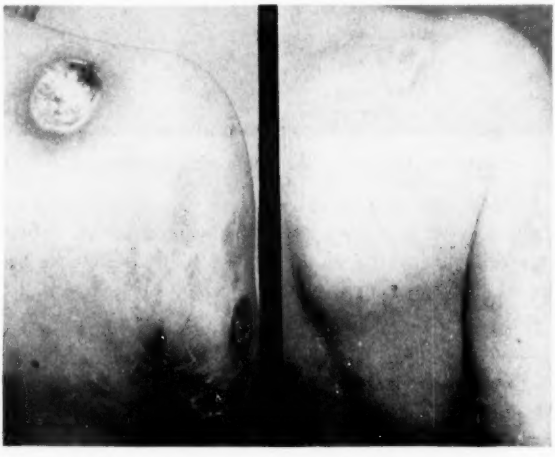

Fig. 4.—Improvement of lesions of mycosis fungoides in two months, following a total of 2,000 rep in several separated treatments.

amenable to therapy. Practically and theoretically, the cathode ray which does not penetrate should not be considered the cause; yet until further experience is obtained and further studies are made, we should treat each patient individually with careful laboratory studies.

PHYSICAL ASPECTS OF HIGH-ENERGY CATHODE RAY THERAPY

The superiority of cathode rays for the treatment of superficial malignant lesions arises from the unique ability to localize their ionizing energy so as to avoid both the irradiation of underlying tissue and the excessive irradiation of the radiosensitive skin. The optimum localization is attained when the high-energy electrons enter normal to the skin surface and when they are of approximately the same energy. A further advantage of cathode ray therapy is that the depth of penetration can be controlled by adjustment of the accelerating voltage.

Figure 5 compares the distribution of ionization below the skin for several different types of particles and radiation, including gamma rays from a radium surface applicator, beta rays from radio-strontium, superficial x-rays, and 2,500,000-volt cathode rays. This study shows that only with the cathode rays is the maximum ionization produced below the epidermal and corium layers of the skin, while at

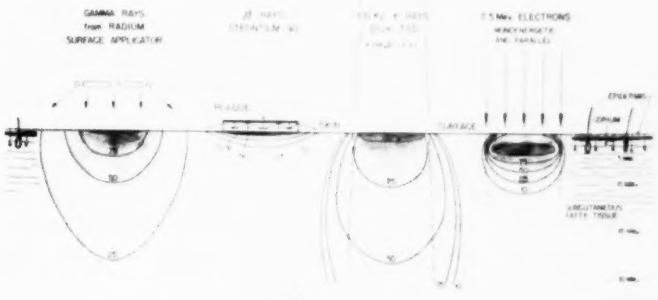

Fig. 5.—Approximate distribution of ionization below the skin produced by gamma rays from a radium surface applicator, beta rays from a plaque of radiostrontium, superficial x-rays of 4 mm. Al HVL at 20 cm. target-skin distance, and 2.5 mev electrons from a constant-potential accelerator.

the same time no effect is produced beyond the limited range of these particles. The maximum penetration into tissue of the 2,500,000-volt electrons is about 12 mm., and the effective range of treatment may be taken at 8 mm. or nearly two-thirds of the maximum range. This distribution of ionization energy can, with electrons, be adjusted for more superficial or deeper-seated surface lesions by correspondingly lowering or raising the electron voltage.

The electron dosage may be measured with a flat thin-walled ionization chamber in a manner similar to the measurement of x-ray dosage and is dependent upon the total number of electrons which have traversed the tissue region. It can be shown that 10^{-9} coulombs of monoenergetic electrons per square centimeter will deliver about 300 rep to the region of maximum ionization. Control of the electron voltage merely determines the depth through which this dose is delivered.

One roentgen equivalent physical (rep) of cathode ray energy is biologically closely equivalent to one roentgen of x-ray energy produced at the same voltage and represents an energy absorption in tissue of about 83 ergs per gram.

A Van de Graff electrostatic accelerator insulated in compressed gas was used to accelerate the electrons to the high constant potentials used in this work. The electrons were permitted to emerge from vacuum into air through a thin aluminum window, and the cathode ray dose was determined by direct measurement of the electron current in the beam.

SUMMARY AND CONCLUSIONS

Electrons can be unusually suitable for the treatment of extensive superficial malignant lesions, provided the electrons are essentially monoenergetic and normally incident upon the skin. These requirements are not met by the beta rays from an applicator such as the radiostrontium applicator but can both be realized with a machine accelerator of the constant-potential type.

Such cathode rays, homogeneous in energy and parallel in direction, would also be ideal for local superficial lesions in that they would avoid damage to underlying tissue and would avoid the caustic effects produced by other forms of ionizing energy on the surrounding perimeter of healthy skin included in the field.

The maximum range of such electrons in tissue is approximately 10 mm. for each 2,000,000 volts of energy. The maximum ionization for monoenergetic electrons from a few hundred kev up to several mev is found at about one-third of this range, and the total depth of effective biological action is about two-thirds of this range.

Five patients suffering from mycosis fungoides were given cathode ray treatments to their entire body surface with virtually complete disappearance of the surface lesions and with no adverse effect on the skin or underlying tissue.

A grant for the further investigation of cathode ray therapy has been received from the Damon Runyon Memorial Fund, and continued support over many years from the Godfrey M. Hyams Trust.

ABSTRACT OF DISCUSSION

DR. JOHN G. TRUMP, Cambridge, Mass.: It is of interest to recall that cathode rays, or high-energy electrons, are actually older than x-rays. Roentgen was experimenting with electrons emitted from a high-voltage discharge tube when he somewhat inadvertently discovered the x-rays for which he has justly become famous. Cathode rays have not become clinically useful because, being tiny negatively charged bundles of matter, they do not penetrate significantly into tissue at ordinary voltages.

As Dr. Fromer pointed out, a 2,000,000-volt electron will penetrate 10 mm. into tissue. There is no ionizing energy delivered beyond this range, and the maximum ionization is found at the 4-mm. depth. At the surface or portal of entry the ionization density is about half the peak value and this results in a remarkable sparing of the radiosensitive skin.

Cathode rays are unique among all forms of ionizing energy in their ability to deliver a localized dose, with no radiation beyond the range which can be predetermined by the voltage, and with less than the maximum on the outermost skin layers.

In dermatological applications, if one is treating a lesion which is only 1 mm. deep, then one would use monoenergetic electrons which have 300 kv of energy. If the lesion is estimated to be 2 mm. deep, 600 kv would be needed. In these cases of mycosis fungoides, the depth of the lesion was about 6 to 8 mm., and therefore about 2,500,000 volts of electron energy was required to distribute a biologically effective dose to the affected tissue depth.

It was Dr. Hare who brought to us the first patient you saw on the slide. Although we had appreciated for over 10 years the unusual suitability of parallel and monoenergetic electrons for superficial therapy, the desperate condition of this patient encouraged us to use electrons clinically

for the first time. Electrons have to be most carefully measured and controlled. In delivering a dose of 300 rep to a lesion, a very minute current of electrons is needed compared to what one uses in x-ray therapy. One thousandth of a microampere will deliver about 300 rep to a square centimeter of skin in one second.

In virtually all the cases that Dr. Fromer described, it was necessary to irradiate the entire skin surface, which was done as he described by passing the patient under this stream of parallel downward directed electrons. This resulted in a complete daily dose to the exposed upward-looking skin in about one minute. Then the patient would be reversed and the posterior aspect treated similarly, as well as the lateral aspects, the region under the arms, and that around the scrotum.

I believe that if cathode rays or high-speed electrons prove to be clinically valuable, it will be possible to develop reasonably compact and flexible sources of electrons for such purposes. The essential features of such sources for the best superficial therapy must include the ability to deliver electrons which are all of the same energy but adjustable to the required tissue penetration, which are proceeding in essentially parallel directions, and which can be delivered over any selected area with a uniform distribution and a precise control of dose. These requirements are best met by a constant-potential machine accelerator.

I should like to acknowledge the stimulation of Dr. Hugh F. Hare in doing this clinical work with high-energy electrons, and the assistance of the Damon Runyon Memorial Fund for Cancer in helping our group at Massachusetts Institute of Technology to perfect the techniques of electron control and measurement.

DR. DANIEL J. KINDEL, Cincinnati: Dermatologists for many years, of course, used roentgen rays as therapy for mycosis fungoides, with concurrent chemotherapy. In the 1940 Yearbook of Dermatology the editors, Wise and Sulzberger, make this comment: "Roentgen rays, combined with injections of sodium arsenate, have achieved"—mind you, this is 1940—"better results than any other forms of therapy. Under such a regimen it has been possible to keep some patients in fairly good condition for ten to twenty years."

Radiation therapy—alone or combined—still offers these patients more help than any other treatment up to the present time. Biologically, the lymphoblastomas—and, particularly, mycosis fungoides—are known to be the most radiation-sensitive classes of tumors. As far as can be determined, the cells composing these tumors are destroyed equally well with low-voltage, soft or relatively nonpenetrating rays, and by supervoltage, hard or high-speed, penetrating wavelengths.

The quality of radiation, whether hard or soft, heterogenous or homogeneous, makes little difference in the lethal effect on the cells themselves, provided the tissue being irradiated is homogeneous and the amount of absorbed energy is the same in both cases.

Biologically, it is well understood that the effect of roentgen rays is due to the ionization produced by the absorption of radiation energy in the tissue, regardless of the quality of the rays themselves. The authors now have pioneered in presenting these remarkable results with cathode rays.

In our own experience in the Department of Dermatology at the University of Cincinnati, we have been able to experimentally control infiltrated lesions of considerable degree—mycosis fungoides—with alpha rays of radon, grenz rays at 30 microns of aluminum HVL, strontium 90, beryllium window radiation at 50 kv, and 100 microns of aluminum, HVL, and, of course, the usual conventional type of x-ray given at 100 kv.

The authors of this very interesting presentation today are taking clinical advantage of the fact that cathode rays are absorbed in the first few millimeters of tissue, and this gives a higher skin tolerance for their therapy, and relatively little or no resulting skin damage. The possible appearance of deep fibrotic changes in the subcutaneous tissue and possibly the muscles close to the skin must be considered.

As time goes on, it becomes more obvious that radiation both above and below the intensity of that which is now generally employed has decided advantages over our conventional form. The experience and knowledge gained in the latter is invaluable as a guide to future applications of the newer modalities.

REFERENCES

Trump, J. G.; Van de Graaff, R. J., and Cloud, R. W.: Cathode Rays for Radiation Therapy, Am. J. Roentgenol. **43**:728-734, 1940.

Brasch, A., and Lange, F.: Aussichten und Möglichkeiten einer Therapie mit schnellen Kathodenstrahlen, Strahlentherapie **51**:119-128, 1934.

Trump, J. G., and Van de Graaff, R. J.: Irradiation of Biological Materials by High Energy Roentgen Rays and Cathode Rays, J. Appl. Physics **19**:599-604, 1948.

Fridell, H. L.; Thomas, C. I., and Krohmer, J. S.: Description of an Sr^{90} Beta-Ray Applicator and Its Use on the Eye, Am. J. Roentgenol. **65**:232-244, 1951.

Trump, J. G., and others: High Energy Electrons for the Treatment of Extensive Superficial Malignant Lesions, Am. J. Roentgen. **69**:623-629, 1953.

COMPARISON OF EFFECTS OF SOAPS AND SYNTHETIC DETERGENTS ON HANDS OF HOUSEWIVES

Clinical Method

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THE EFFECT of household washing products on the skin is a subject of importance and concern not only to the housewife but to the physician and the manufacturer as well.

In recent years there has been in this country a decided trend toward the synthetic detergent products for household use. The amount used has increased from less than 1 lb. (0.5 kg.) per person, in 1942, to almost 10 lb. (4.5 kg.) per person, in 1951.[1] Almost two-thirds of the package household washing products sold today are synthetic detergents. This great increase in the use of synthetic detergents since World War II has been due largely to the introduction of all-purpose synthetic detergents. The all-purpose synthetic products are analogous to the all-purpose soaps, in that they contain certain builders, mostly inorganic phosphates, in addition to the active synthetic detergent to make them clean better.

Because of the almost universal use of synthetic detergents and the wide variety of products used or proposed for use in them, it is important to have available methods for comparing their effects on the skin which are valid, reliable, and realistic.

About 10 years ago Kooyman and Snyder [2] described a modification of the patch test and an arm immersion test for comparing the mildness of different types of soap products. In these tests exposure to solutions of soap products was exaggerated over that experienced by a housewife in normal use of the product in one or more of the following ways: (1) extended time of contact with soap solution; (2) higher temperature of soap solution; (3) greater concentration of soap in solution.

Exposure was exaggerated so that visible irritation would be produced on most of the experimental subjects by at least one of the products under comparison.

1. Disappearance of Soap and Synthetic Detergents, The Fats and Oils Situation, Bureau of Agricultural Economics, U. S. Department of Agriculture, May-June, 1951. Snell, F. D.: Synthetic Detergents, Chem. & Engineering News **30**:30 (Jan. 7) 1952.

2. Kooyman, D. J., and Snyder, F. H.: Tests for the Mildness of Soaps, Arch. Dermat. & Syph. **46**:846-855 (Dec.) 1942.

So long as these tests were used to compare soap products, the results were in agreement with the experience of housewives who used the products, i. e., fine-fabric or toilet soaps were found to be milder in their action on the skin than all-purpose and hard-water soaps. When patch and arm immersion tests were used to compare products as different in composition as soaps and synthetic detergents, the results did not always agree with the experience of housewives.

A more reliable and realistic method, it seemed, would be to examine the hands of a group of housewives after they had used the different products in the usual manner in the home.

The purpose of this paper is to present a method for comparing the average response of the skin of typical users to soaps or synthetic detergents under conditions of frequent and regular use in the home, and to present some typical data. The first of these tests was made almost 10 years ago. The procedure we describe was evolved in the course of more than a dozen tests made since then, in which more than 5,000 housewives participated.

PLAN OF THE TEST

Essentially, the test consists of having large numbers of women use the products at home for a period of time and checking their reactions by a careful examination of the skin of their hands and arms before and after the test period. Between 200 and 300 women use each test product. Such a relatively large group provides a rather representative sample of the population as to skin type and condition and is of good size for statistical significance. The usual test period is two weeks, although we have made tests with a two-month test period. Two or more products can be compared at a time. In the tests we have made, usually three to six products were compared.

Experimental Subjects.—Subjects for these surveys were typical housewives. No selection of subjects was made on the basis of skin type, complexion, or age. We specified that during the test the women must have a reasonable exposure to the detergent solutions, i. e., they must wash dishes for a family of three or more persons at least twice a day and without the use of rubber gloves or an automatic dishwasher. They were instructed to do all their regular dishwashing using only the test product given them.

Interview.—Prior to the first examination of the hands, each woman was interviewed by a secretary for information regarding her age, size of her family, cleaning methods and habits, and her opinion as to the mildness of the product she had been using.

Examination and Grading.—The hands were next examined by the dermatologist,[3] grossly and microscopically by means of a wide-angle binocular microscope, as suggested by Goldman and Younker.[4] A grade was given for the general condition of the hands, based on dryness, scaling, redness, and fissuring, which are the cardinal

3. Eleven dermatologists practicing in the United States or Canada have collaborated in one or more of these tests.

4. Goldman, L., and Younker, W.: Studies in Microscopy of the Surface of the Skin: Preliminary Report of Technics, J. Invest. Dermat. **9**:11-16 (July) 1947.

features of cutaneous soap damage, according to Sulzberger and Baer.[5] The grading scale was in units of 10 from 0 to 100. If the hands were soft, smooth, and of normal color and appearance, they were given a grade of 100. At the other end of the scale, hands which exhibited extreme dryness and redness, with deep fissures, were given a grade of 0.

To make the examination as objective as possible, a stenographer recorded the grades and pertinent comments of the examining dermatologist. In this way, he had no cause to refer to the data sheet, and consequently had no knowledge of the previously assigned grades or of the products used.

At the end of the examination each subject was given a test product to use during the next two weeks. These were issued in blank packages bearing only an identifying code letter.

TABLE 1.—*Grades Assigned for Condition of Skin After Test with Three Soaps*

	Number of Women Given Each Skin Grade Before and After Test Period with Each Product					
	Fine-Fabric Soap		All-Purpose Soap A *		All-Purpose Soap B *	
Skin Grade	Before	After	Before	After	Before	After
100 (Best)	13	28	18	19	15	19
90	43	37	43	49	43	38
80	55	62	55	63	54	46
70	54	56	58	58	55	61
60	32	24	32	21	29	32
50	18	17	18	15	22	15
40	14	7	13	12	9	16
30	3	3	4	5	4	5
20	2	0	1	0	1	2
10	0	0	2	2	3	1
0 (Poorest)	1	1	0	0	0	0
Total number of women in test	235		244		235	
Mean grade	71.75	75.19	72.25	74.06	71.96	71.40
Average change in grade	+3.44		+1.81		−0.56	
Average temperature			53 F.	44 F.		

* All-purpose soap A contained more soap and less builder than all-purpose soap B

RESULTS WITH SOAP PRODUCTS

As was pointed out in the introduction, many years of experience with soap products have shown that fine-fabric soaps or soaps without builder are somewhat milder in their action on the skin than all-purpose or laundry soaps.

Results of a test in which three different popular soap products were compared are given in Table 1. One product was a fine-fabric soap, the other two were all-purpose soaps differing in the amount of builder they contained. In spite of the fact that the average temperature for the three days prior to examination was lower after the test period than before (the test was run in Cincinnati during the winter season), the average condition of the hands of the women using fine-fabric soap improved. This is not surprising, since most of the housewives had been using dishwashing products less mild than fine-fabric soaps before the test. Improvement also was found in the average condition of the hands of subjects using the all-purpose soap A, while those using all-purpose product B showed a lower average grade. Statis-

5. Sulzberger, M. B., and Baer, R. L.: Unusual or Abnormal Effects of Soap on the "Normal Skin," in Medical Uses of Soap: A Symposium, edited by M. Fishbein, Philadelphia, J. B. Lippincott Company, 1945, p. 56.

tically, the difference between the fine-fabric soap and the all-purpose soap B is significant, but the all-purpose soap A is not significantly different from the other two products with which it was compared. An interesting point is that a majority of the housewives showed little or no change in the condition of their hands during the test, as is shown graphically in Chart 1.

Housewives' Appraisal of Test Products.—Users may experience subjective skin symptoms described as "drawn," "tight," or "itchy," which may not be apparent

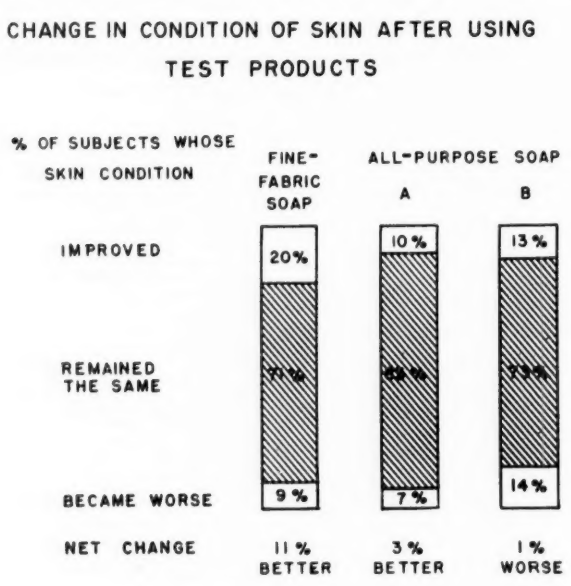

Chart 1

TABLE 2.—*Housewives' Rating of Relative Effects of Products on Hands*

Housewives' Rating of Product	Grade	Number of Women Giving Each Rating: Fine-Fabric Soap	All-Purpose Soap A	All-Purpose Soap B
Very easy on skin	100	54	43	28
Moderately easy on skin	80	56	39	35
Not hard on skin	60	67	69	62
Slightly hard on skin	40	31	49	63
Moderately hard on skin	20	16	21	24
Very hard on skin	0	11	23	23
Total number of women	..	235	244	235
Average rating of test product	..	65.8	57.1	52.4

on examination. Recognizing this, the women were asked during each interview to select the phrase which most accurately described the action of the product they were using from the statements given in Tables 2 and 4.

Table 2 shows the test subjects' rating of the same three soap products listed in Table 1. The average scores for the housewives' appraisal rank the test products

in the same order as the grades assigned by the examiners. Statistically, the fine-fabric soap and the all-purpose soap A were rated significantly better than the all-purpose soap B by the housewives.

A comparison of these three soap products in a clinical use test thus gave results which are in general agreement with the experience of many years of normal use of these products in the home, as well as with the ratings of housewives after using the products from unlabeled packages in the test.

COMPARISON OF AN ALL-PURPOSE SYNTHETIC DETERGENT WITH SOAP PRODUCTS

The following results are taken from another clinical test conducted at a different time, using no subjects who had participated in a previous test of this kind. Three products were compared for dishwashing—the two all-purpose soaps used in the

TABLE 3.—*Grades Assigned for Condition of Skin After Test with Soaps and Synthetic Detergent*

	Number of Women Given Each Skin Grade Before and After Test Period with Each Product					
	All-Purpose Soap A		All-Purpose Synthetic		All-Purpose Soap B	
Skin Grade	Before	After	Before	After	Before	After
100 (Best)	12	10	14	25	8	7
90	34	40	43	33	41	41
80	62	72	61	57	62	69
70	81	79	75	82	87	77
60	33	22	30	30	29	34
50	14	13	12	13	13	8
40	23	26	25	25	24	26
30	10	9	7	4	4	4
20	2	0	0	0	0	1
10	0	1	3	0	1	2
0 (Poorest)	1	0	0	1	0	0
Total number of women in test	272	272	270	270	269	269
Mean grade	69.23	70.51	70.51	71.62	70.71	70.41
Average change in grade	+1.28		+1.11		−0.30	
Average temperature			36 F.	33 F.		

test reported in Table 1, and the most widely used all-purpose synthetic detergent. Grades assigned for skin conditions before and after the test period are given in Table 3.

From the figures for change in average skin grade, it is apparent that the responses were similar for the three products. Slight improvement occurred in the groups using all-purpose soap A and the all-purpose synthetic detergent; no improvement took place in the group using all-purpose soap B. The differences among the products, however, are not statistically significant.

A graphic comparison of the changes experienced by individual subjects in this test is given in Chart 2. Here again the similarities are more impressive than the differences among the three products.

Housewives' Appraisal of the Action of the Products on Skin.—A tabulation of the housewives' ratings for action on skin of these three products is given in Table 4. Their grades rank the products in the same order as did the grades of the

examiners (Table 3). Both the all-purpose soap A and the all-purpose synthetic were rated better than the all-purpose soap B.

UNUSUAL SKIN RESPONSES

In any large group of women, such as were required for these tests, it would not be unlikely that in some a dermatitis would develop during the test. A few women

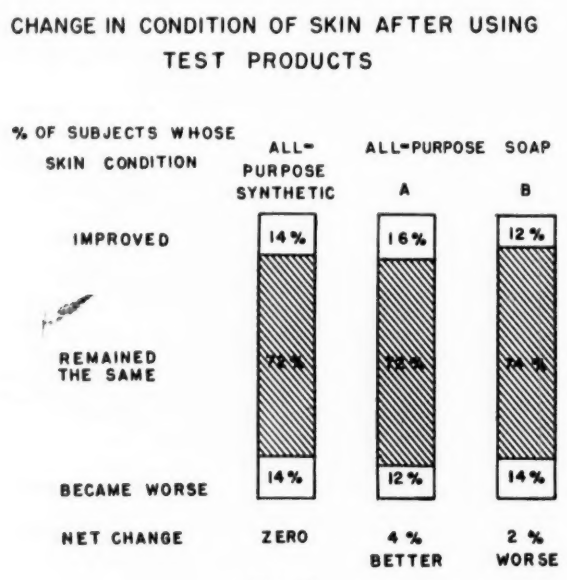

Chart 2

TABLE 4.—*Housewives' Rating of Relative Effects of Products on Hands*

Housewives' Rating of Product	Grade	Number of Women Giving Each Rating: All-Purpose Soap A	All-Purpose Synthetic	All-Purpose Soap B
Very easy on skin	100	89	74	62
Moderately easy on skin	80	72	77	62
Not hard on skin	60	44	36	48
Slightly hard on skin	40	33	52	49
Moderately hard on skin	20	20	17	28
Very hard on skin	0	14	14	20
Total number of women	..	272	270	269
Average rating of test products	..	69.9	67.2	61.6

who appeared at the initial examination with acute dermatitis of the hands were advised against exposing their hands to washing solutions of any kind and were excluded from the test. However, none was excluded from the test only because of a history of dermatitis of the hands. Some housewives with chronic lesions of psoriasis, nummular eczema, or dyshidrosis were included among the test subjects.

Of the more than 5,000 housewives who participated in these tests, 5 had to discontinue because of eruptions on the hands. All these eruptions were recurrences

in subjects who gave histories of previous skin trouble. The test product used by these five persons was in some instances a soap, in others a synthetic detergent. From these results it seems that in the exceptional person, a recurrence of a pre-existing dermatitis may be induced by either a soap or a synthetic detergent. There was no evidence from these tests that the use of soap or synthetic detergents caused a sensitization in these subjects. The low incidence of dermatitis would indicate that if these products are sensitizers, they must have a very low index of sensitization.

DISCUSSION

Some Factors Which Influence Skin Condition.—In addition to the product used for dishwashing, there are a number of other factors which can and do affect the condition of the skin as seen on the day of examination. Some of these are discussed in the following paragraphs.

Inherent Differences in Type of Skin.—In rather large groups of housewives it is not unusual to find some with hands that are chronically dry and fissured. Also, some have hands that are very red or very pale because of disturbance of the peripheral circulation. These conditions may be quite unaffected by the product used for dishwashing. They will, however, influence the grade assigned for skin condition at the time of examination. Conditions which are chronic or of a permanent nature will, of course, be present at all examinations and will not cause the grade to change during the test.

Difference in Amount of Exposure in Dishwashing.—Women who washed dishes only occasionally before the test and then washed them regularly three or four times a day during the test often showed a lower grade for skin condition even though the product was the same as that she was using before the test. The amount of exposure in dishwashing obviously can vary with the amount of entertaining at home or the number of dinners eaten out. By the use of large numbers of women in each group, chance tends to keep these factors the same for each group.

Exposure to Detergents Other Than Test Products.—While dishwashing is usually the most important exposure to detergent solutions (at least 60% of total exposure), there are many cleaning operations in housekeeping which can have important effects on the condition of the hands. Some of these are laundering, fine fabric or hand laundering, shampooing, car washing, window washing, and housecleaning. In the data presented it was assumed that in the large groups a similar proportion of miscellaneous cleaning was done in each.

Exposure to Materials Other Than Detergents.—Organic solvents, such as those present in dry cleansers or spot removers, turpentine or other paint vehicles, paint removers, and gasoline, are all effective in defatting the skin exposed to them. Some subjects may have used these materials during the test, but here again it was assumed that the incidence was similar in all the groups.

The juices of fruits and vegetables may cause dryness and fissuring, particularly on the thumb and fingers most exposed to them in paring, peeling, or cutting. This was usually a chronic condition and did not change appreciably during the test.

Change in Weather Conditions.—A marked change in temperature and the associated change in relative humidity has an important effect on the apparent and subjective condition of the skin. As the temperature falls below freezing, the indoor

relative humidity becomes lower, and the skin becomes drier. This effect has also been observed and investigated by Gaul and Underwood.[6]

In the clinical test comparing soaps (Table 1) the average temperature for the day of preliminary examination and the two previous days was 53 F., and it was 44 F. for the final examination. In the soap vs. synthetic detergent comparisons (Table 3) these average temperatures were 36 F. and 33 F. respectively. The lower average temperature during the second test could account for the somewhat lower initial average grades for skin condition in this test. Since the weather or temperature factor is similar for all women examined on the same day, this effect is compensated for by having the test products equally represented on any given examination day.

CONCLUSION

The clinical use test, when conducted on a sufficiently large scale, employing at least 200 women for each product compared, is a realistic procedure for comparing the relative effects of household washing products on the skin. The results of such tests have been in general agreement with the independent appraisal of housewives, who used the products in a normal manner for washing operations in the home.

SUMMARY

1. A procedure for determining the relative condition of the skin of housewives' hands after using different detergents for regular household washing operations is described. It is based on gross and microscopic examination of the subjects' hands and lower arms before and after two weeks' use of the test products. Data are presented which are typical of those obtained in more than a dozen tests of this kind.

2. The relative ratings of the products as determined in this type of clinical test are in general agreement with those based on appraisals by the women who used them.

3. Among the products for which test data are given, fine-fabric soap was associated with the best general skin condition of the hands. An all-purpose synthetic detergent and one all-purpose soap were found to be similar in this respect and next best, and both were somewhat better than a second all-purpose soap. In no case was the difference between products large.

4. The incidence of dermatitis among the more than 5,000 housewives who participated in tests of this kind was about 1 in 1,000. All cases of dermatitis were recurrences of previously existing skin trouble and occurred with both soap and synthetic test products. The specific cause of the dermatitis in these cases was not determined.

Madison, Wis.

6. Gaul, L. E., and Underwood, G. B.: Relation of Dew Point and Barometric Pressure to Chapping of Normal Skin, J. Invest. Derm. **19**:9-19 (July) 1952.

QUINACRINE HYDROCHLORIDE (ATABRINE) IN THE TREATMENT OF LUPUS ERYTHEMATOSUS

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IN A PRELIMINARY report [1] we indicated that quinacrine hydrochloride (atabrine) has a definite place in the treatment of patients with lupus erythematosus—especially in those with the chronic discoid variety. We wish now to report on our additional experience and longer observation of the patients treated.

Apparently the English-speaking world first became aware of the value of quinacrine in the treatment of patients with lupus erythematosus from the report of Page,[2] although such therapy had been described 10 years earlier by Prokoptchouk,[3] Sorinson,[4] Popoff and Kutintscheff,[5] and Ottolenghi and Lodigiani.[6] During the past year the case presentations at society meetings and a few reports in the literature * indicate general agreement that quinacrine is an efficient drug for the treatment of chronic discoid lupus erythematosus.

Prokoptchouk [3] successfully treated 35 patients with lupus erythematosus by giving 100 mg. of quinacrine hydrochloride three times daily for 10 days, following this by a rest period of 10 or 11 days, then by a repetition of the course of quinacrine, and another rest period. He considered that better results were obtained when the disease was of short duration and he noted that the skin, especially of the face and hands, became yellow with treatment. Sorinson [4] treated 70 patients by Prokoptchouk's method of administering quinacrine. The majority required five or more courses of quinacrine to obtain benefit. Of the 51 patients who received a total of 12 gm. or more of the drug, 12 achieved "complete cure," 17 marked improvement, and 10 showed some degree of improvement, while the remaining 12 had no benefit or no effect. He found that the favorable results were usually evident after the first two courses of treatment. Sorinson also stated that quinacrine hydrochloride (Acrichin) was most effective in the erythematosus type of lupus erythematosus and that the percentage of cures in the discoid type was lower. Forty-one per cent of patients with the erythematous type were completely cured, while an equal number showed marked improvement. He also correlated the degree of yellowing of the skin with the amount of improvement and found that

From the Section of Dermatology, Mayo Clinic.

Read at the Seventy-Third Annual Meeting of the American Dermatological Association, Inc., Lake Placid, N. Y., June 11, 1953.

* References 7 through 10.

TABLE 1.—*Duration of Lupus Erythematosus Prior to Administration of Quinacrine*

Duration, Yr.	Females	Males	Total
0- 1	2	1	3
1- 2	1	1	2
2- 5	11	8	19
5-10	5	7	12
10-15	9	1	10
15+	11	3	14
Total	39	21	60

TABLE 2.—*Age at Onset of Lupus Erythematosus*

Age, Yr.	Females	Males	Total
0- 9	0	1	1
10-19	3	0	3
20-29	15	7	22
30-39	12	4	16
40-49	6	8	14
50-59	3	1	4
60+	0	0	0
Total	39	21	60

TABLE 3.—*Age Therapy with Quinacrine Begun*

Age, Yr.	Females	Males	Total
0- 9	0	1	1
10-19	0	0	0
20-29	2	2	4
30-39	13	6	19
40-49	16	5	21
50-59	5	5	10
60+	3	2	5
Total	39	21	60

TABLE 4.—*Subsequent Course of Twenty-One Patients Who Stopped Using Quinacrine*

Time After Treatment Discontinued	Recurrence	No Recurrence
2-4 wk	2	0
1-3 mo	4	6
3-6 mo	3	2
6+ mo	1	3
Total	10	11

the greatest degree of improvement was found in those patients who were the most yellow. Popoff and Kutintscheff [5] successfully treated six patients in a similar manner.

Ottolenghi and Lodigiani [6] infiltrated the plaques of lupus erythematosus with solutions containing 5 to 10% of quinacrine. Approximately 33% of the 20 patients recovered within three months; less than 33% had apparent recoveries but relapses occurred within three months; 5% did not have any successful results, and the remainder were improved. It was indicated that the patients who recovered showed less scarring than those treated with carbon dioxide alone.

We have treated most of our patients according to the suggestions of Page [2] and have given 100 mg. of quinacrine hydrochloride three times daily for the first week, 100 mg. twice daily the second week, then 100 mg. daily. Nevertheless, considerable variation exists in individual dosages which have been given and maintained. Some patients have received as much as 400 mg., while others were given as little as 100 mg. daily.

We have treated other patients not included in the group covered by this report with such antimalarial drugs as chloroquine diphosphate and primaquine, but the number of patients is small and the length of observations too short to permit evaluation of the data.

MATERIAL

During 1952, we treated with quinacrine 60 patients who had lupus erythematosus. Fifty-five of these patients had the chronic discoid form of the disease and five (three men and two women) had moderate systematic manifestations of lupus erythematosus. Thirty-nine patients were women and 21 were men. The duration of the lupus erythematosus varied considerably as noted in Table 1, while Tables 2 and 3 give the patients' age at onset of lupus erythematosus and the age at which treatment with quinacrine was begun.

These tables indicate that most of the patients had the disease for many years prior to treatment with quinacrine; also they show the wide diversity of age at which the disease may begin, and the fact that, as a rule, lupus erythematosus tends to develop later in life in men more often than in women. Our youngest patient, a boy 3 years of age who had had his disease for two years, is an obvious exception. The few patients with the systematic forms of lupus erythematosus had had the disease for many years (7 to 20 years).

Only eight patients had received no previous treatment while the remainder of our patients had received many types of therapy previous to the administration of quinacrine. These included gold, bismuth, arsenic, quinine, iodides, derivatives of pantothenic acid paraaminobenzoic acid, vitamins B, B_{12}, and E, liver extract, carbon dioxide snow, cortisone, corticotropin, androgens, estrogens, and local preparations, including protectives against light, and even roentgen therapy.

RESULTS

In the appraisal of the results of treatment, it is apparent that the only parts of the skin lesion that can be expected to show improvement are the erythema and the inflammatory infiltrate. It is not expected that the scars will change. Thus

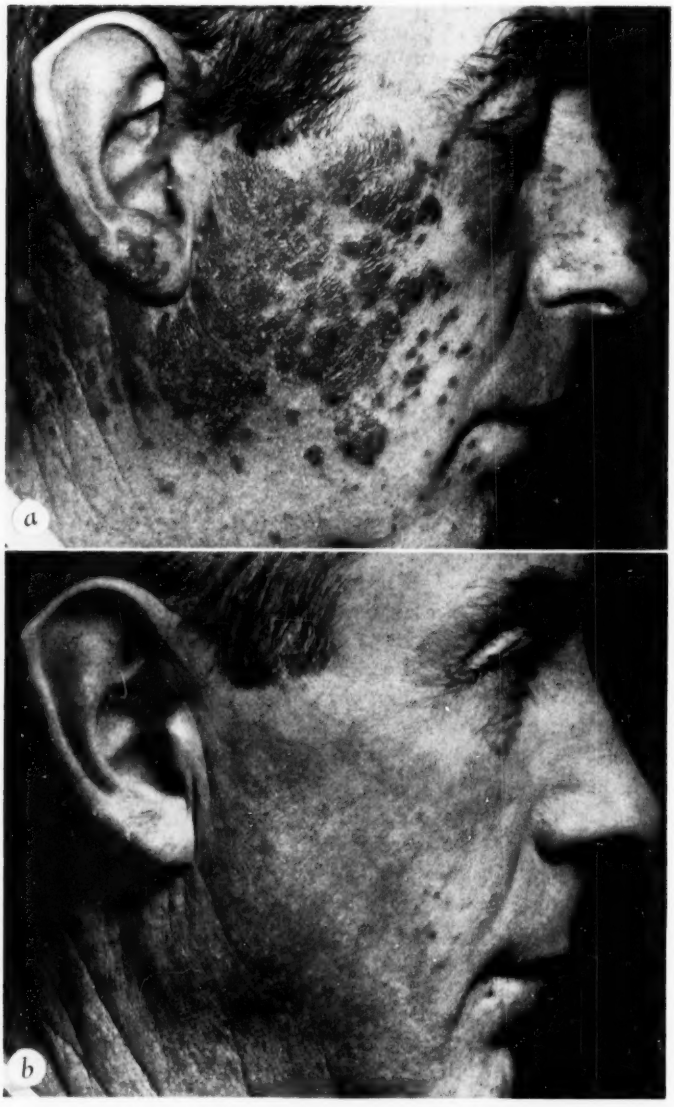

Fig. 1.—Chronic discoid lupus erythematosus of four years' duration. (*a*) Prior to treatment with quinacrine. (*b*) Clearing of eruption with therapy with quinacrine for 62 days.

our results (Figs. 1 to 4) indicate that the activity of the cutaneous lesions has decreased, the extent to which this has occurred, and for how long the improvement has remained.

Of the 55 patients with chronic discoid lupus erythematosus, 52 have been followed to April, 1953, either directly or by correspondence. The results obtained are as follows: 11 patients were 0 to 25% improved (1 of these reported that he became worse); 9 were 25 to 75% improved; 15 were more than 75% improved, but the disease was not arrested, and 17 had complete arrest of the disease.

Twenty-one of the patients had discontinued receiving quinacrine and their subsequent courses are given in Table 4.

Several of the patients who had been receiving low maintenance doses of 50 to 100 mg. of quinacrine daily noted that after exposure to the sun this spring some of the lesions of lupus erythematosus again became active after several

Fig. 2.—Lupus erythematosus. (*a*) Appearance prior to therapy with quinacrine. (*b*) On 21st day of therapy. (*c*) Appearance five months after treatment with quinacrine was begun.

months of inactivity. The recurrent lesions were found most often on the lower lip, lobe of the ear, and nose.

Three patients who achieved excellent results from the first course of therapy but who had recurrences responded more slowly and less satisfactorily to the second course of quinacrine even when higher doses were given.

UNFAVORABLE EFFECTS

It appears definite from our experience that administration of quinacrine is of great value in the treatment of the chronic discoid types of lupus erythematosus (Figs. 1 to 4), and at the same time, the incidence of untoward reactions is low. The yellow color of the skin, which we do not classify as an untoward incident and which was present in the majority of patients, was of little concern to them and disappeared in from a few weeks to two months after treatment was discontinued. Fluorescence of the nails, teeth, and sweat ducts, as had been noted previously †

† References 11 through 13.

Fig. 3.—(*a* and *c*) Appearance in 1950, showing no response to other methods of therapy. Treatment with quinacrine was begun in June, 1952, and discontinued in September, 1952. (*b* and *d*) Appearance seven months after treatment with quinacrine was discontinued.

subsided much more slowly—a matter of several months. Occasionally a gastrointestinal upset of some degree occurred in patients receiving 300 to 400 mg. of quinacrine daily, but this subsided in all instances when the daily dose of the drug was reduced. In two patients reactions of anxiety and increased nervousness developed, but in none of our patients with chronic discoid lupus erythematosus did other undesirable and serious effects of therapy with quinacrine appear.

In this series the severe untoward effects appeared in patients with systemic forms of the disease and with laboratory evidence of systemic involvement. Interestingly enough, reactions developed in all of the patients who had systemic lupus erythematosus but three of them had benefit from quinacrine before the undesirable incident occurred. A generalized pityriasis-rosea-like eruption developed in one case after quinacrine had been given for more than two months. This subsided within a month after treatment with quinacrine was discontinued. It was estimated that the eruption of lupus had improved 75% before the reaction appeared. There was no exacerbation of the lupus erythematosus during the pityriasis-rosea-like reactions, nor did it become worse in the next three months.

Fig. 4.—Lupus erythematosus of the nose of 13 years' duration. (*a*) Prior to treatment with quinacrine. Verrucous hyperplasia may be noted. (*b*) Appearance four months later while quinacrine was still being received. (*c*) Appearance seven months after therapy was begun. Disappearance of verrucous hyperplasia may be noted.

Another patient had received quinacrine for two and a half months and showed much improvement in the skin lesions of lupus erythematosus but a lichenoid eruption developed, which persisted for more than four months before eventually clearing. When the lichenoid reaction subsided, it was noted that there was no further cutaneous evidence of lupus erythematosus, and the laboratory reflections of the disease were improved as well.

A third patient who had taken quinacrine continuously for four months achieved a complete arrest of the lupus erythematosus, but then a lichenoid cutaneous reaction developed. Treatment with quinacrine was discontinued, but it took three months for the skin to clear, and six months later there was reactivation of the lupus erythematosus.

Another patient had received quinacrine for six months with but little change on the skin; later there was an extension of the lupus erythematosus with additional features suggesting a mild superimposed lichenoid reaction. Two months later there was still further extension of the lupus erythematosus.

None of these four patients have had any of the serious sequelae from quinacrine noted in World War II, such as followed the New Guinea variety of lichenoid dermatitis, namely, alopecia, hyperpigmentation, anidrosis, or scarring.

The fifth patient had received quinacrine for six weeks when leucopenia with neutropenia and thrombocytopenia developed, together with a febrile reaction and increased sedimentation rate. After treatment with quinacrine was discontinued, the temperature gradually became normal, the sedimentation rate fell, and the counts of the leucocytes, granulocytes, and thrombocytes rose to the pretreatment levels, which had been abnormal. The lupus erythematosus in this patient was not benefited by quinacrine.

In view of these experiences, we believe that therapy with quinacrine of patients with systemic lupus erythematosus is hazardous. Nevertheless, other investigators have made favorable reports on such treatment in this variety of the disease.

It is necessary, however, to remember the potential serious sequelae of therapy with quinacrine. These reactions are similar to those of gold, arsenic, and, to a lesser degree, bismuth. We consider, however, that the incidence of reactions from quinacrine is less frequent than that from the heavy metals. The skin participates with the greatest frequency in these undesirable reactions usually in one of the following ways: an eruption which simulates either lichen planus, pityriasis rosea, seborrheic dermatitis, or dyshidrosis. The lichen-planus-like reaction is the most severe and the slowest to subside and may be followed by hyperpigmentation, anidrosis, scarring, and alopecia. The developmental period of the lichenoid reaction is long. In a series of patients studied previously [14] it varied from six weeks to nine months; the greatest number of reactions appeared three to six months after treatment with quinacrine was begun. Untoward reactions may involve the hematopoietic system, in the form of an aplastic anemia, the central nervous system, the gastrointestinal system, and the liver. We recommend that erythrocyte and leucocyte counts and determination of hemoglobin be done each week while patients remain under treatment.

COMMENT

No one, to our knowledge, knows the reason why patients with lupus erythematosus respond well to the administration of quinacrine. It has been suggested that the fluorescence produced by quinacrine‡ interferes with the activating effect of the sunlight on the lupus erythematosus. In this connection it has been thought that yellowing of the skin by quinacrine was necessary in the production of good results. Our experience has been to the contrary, as we have seen excellent results without perceptible yellowing of the skin. A demonstrable fluorescence may be present long before the skin becomes yellow. Lobitz [15] used the fluorescence as a means of controlling the dosage of quinacrine, as he maintained the daily dose of quinacrine so that the distal portion of the palmar sweat ducts were fluorescent although the skin was not yellow. Increased fluorescence also may be noted in the active portions of the plaques of lupus erythematosus.

In the patients who derive good results from quinacrine, the significant improvement appears within the first four to six weeks of therapy. In other words, if some beneficial results are not apparent in the first month of treatment, it is doubtful that any marked degree of benefit will be obtained by the patient.

‡ References 11 through 13.

As yet we are not certain which of the various dosage schedules is most effective and neither have we decided whether the short or long courses of therapy are most beneficial. The individual requirements of patients vary considerably. In some patients the signs of activity in the skin lesions disappear on doses of 100 mg. of quinacrine daily, while in others larger doses are required. When complete arrest or maximal improvement appears, the result may be maintained on doses as low as 50 mg. daily. We do not know that permanent cure has been achieved in any of our patients, but in some of them the remissions have lasted for six months after treatment with quinacrine has been discontinued.

SUMMARY

We believe that the results of treatment with quinacrine of patients with the chronic discoid variety of lupus erythematosus have been satisfactory, and our experience confirms the findings of previous and contemporary investigators. In contrast, for patients with widespread cutaneous manifestations of lupus erythematosus and for those in whom there is also laboratory evidence of the systemic type of the disease, the results of treatment with quinacrine have not been satisfactory. In patients with chronic discoid lupus erythematosus the incidence of untoward reactions from therapy has been low. Perceptible yellowing of the skin is not a requirement in the production of good results.

REFERENCES

1. O'Leary, P. A.; Brunsting, L. A., and Kierland, R. R.: Quinacrine (Atabrine) Hydrochloride in Treatment of Discoid Lupus Erythematosus A. M. A. Arch. Dermat. & Syph. **67**:633-634 (June) 1953.

2. Page, F.: Treatment of Lupus Erythematosus with Mepacrine, Lancet **2**:755-758 (Oct. 27) 1951.

3. Prokoptchouk, A. J.: Traitement du loup érythémateux par l'acriquine, abstracted, Zentralbl. Haut- u. Geschlechtskr. **66**:112, 1940-1941.

4. Sorinson, N. S.: Acrichin in Therapy of Lupus Erythematosus, Vrach. delo. **23**:441-446, 1941.

5. Popoff, L., and Kutintscheff, M.: Case Reports, abstracted, Dermat. Wchnschr. **116**:186 (March) 1943.

6. Ottolenghi and Lodigiani, F.: Risultati col trattamento del lupus eritematoso fissco con iniezioni intradermiche di derivati acridinici, abstracted, Excerpta Med. XIII **4**:384, 1950.

7. Sommerville, J.; Devine, D. C., and Logan, J. C. P.: Lupus Erythematosus Treated with Mepacrine, Brit. J. Dermat. **64**:417-419 (Nov.) 1952.

8. Cramer, J. A., and Lewis, G. M.: Atabrine in the Treatment of Discoid Lupus Erythematosus, J. Invest. Dermat. **19**:393-395 (Dec.) 1952.

9. Sawicky, H. H.; Kanof, N. B.; Silverberg, M. G.; Braitman, M., and Kalish, B.: Therapeutic Assays of the Skin and Cancer Unit of the New York University Hospital; Assay VII, Quinacrine Hydrochloride (Atabrine Hydrochloride) for Chronic Discoid Lupus Erythematosus, J. Invest. Dermat. **19**:397-404 (Dec.) 1952.

10. Wells, G. C.: Treatment of Chronic Discoid Lupus Erythematosus with Atabrine, J. Invest. Dermat. **19**:405-407 (Dec.) 1952.

11. Ginsberg, J. E., and Shallenberger, P. L.: Wood's Light Fluorescence Phenomenon in Quinacrine Medication, J. A. M. A. **131**:808-809 (July 6) 1946.

12. Kierland, R. R.; Sheard, C.; Mason, H. L., and Lobitz, W. C.: Fluorescence of Nails from Quinacrine Hydrochloride, J. A. M. A. **131**:809-810 (July 6) 1946.

13. Herrmann, F., and Miller, O. B.: Pharmacologic and Pathogenetic Effects of Mepacrine Chloride (Atabrine) upon the Human Skin: I. Clinical and Experimental Observations, Acta dermat.-venereol. **32**:304-332, 1952.

14. Kierland, R. R.: Drug Eruption Due to Atabrine and Resembling Lichen Planus, Proc. Staff Meet., Mayo Clin. **21**:404-408 (Oct. 16) 1946.

15. Lobitz, W. D.: Personal communication to the authors.

ABSTRACT OF DISCUSSION

DR. HERBERT RATTNER, Chicago: The report of Dr. Kierland and his associates is of interest and importance in several respects.

It was a surprise, first of all, to learn that the treatment had been first recommended by a Russian as long ago as 1940 and that it escaped our notice. In extenuation, it could be said that at the time our energies were more properly spent on study of foreign political reports rather than the medical, and that since then and for obvious reasons, we no longer look for advances in the medicine of totalitarian countries. However, since quinacrine causes the patients to turn yellow rather than red, we should have no qualms about using it!

It was interesting also to note the tone of conservatism in Dr. Kierland's report, despite the good results that were obtained in a sizable number of cases. Only once was the term "cure" used, and that was to emphasize that they could not speak in terms of its permanency—rather, they mentioned arrests, or benefits, and the fact that the drug appears to have great value, is efficient, has a definite place, and so on. That seems to be the general opinion, for most of us, I think, feel that though quinacrine is probably the best drug we now have for the treatment of localized cutaneous lupus erythematosus, yet it seems to have certain limitations, aside from the well-known side-effects.

Though practically all patients show improvement, in many this improvement continues only up to a point. It is the general experience, too, that, as Dr. Kierland reported, the incidence of untoward effects is rather low; improvement is noted within three or four weeks of treatment or not at all; improvement may occur without the skin turning yellow; the action of the drug is not affected adversely by previous treatment with other drugs, by the age of the patient or the sex, and not too much by the age of the lesion; recurrent lesions do not respond as quickly to treatment as do the first lesions, and the dosage has to be varied. The drug, I was surprised to learn, may be infiltrated into the lesions when necessary.

Dr. Kierland found the treatment hazardous for patients with systemic lupus erythematosus, although some of his patients benefited temporarily. Our experience at the Cook County Hospital was even more disappointing, for in all five of our cases of systemic type which Dr. Bluefarb undertook to treat there was almost immediate deterioration. We, too, have begun to use other antimalarial drugs, but our experience is also too small to permit evaluation.

The perplexing thing is, as Dr. Kierland has noted, that no rationale has as yet been advanced to explain the beneficial action of quinacrine on discoid lupus erythematosus. He suggests that perhaps the fluorescence produced by quinacrine interferes with the activating effect of sunlight on it. Sulzberger and Baer in the current "Year Book of Dermatology and Syphilology" mentioned other possibilities: antimicrobial effects, metabolic effects, liver damage, competition with essentials of enzyme or coenzyme systems, cortisone-like actions, reticuloendothelial blockade, or nonspecific immunological effect. Perhaps quinacrine, like quinine, affects blood sludge, and perhaps no rationale will be forthcoming until the cause of lupus erythematosus is determined and the disease can be reproduced in experimental animals.

Dr. Kierland's detailed report of results in 60 cases has practical value. It is significant, I think, that the authors formulated impressions rather than conclusions from their results.

DR. ARTHUR R. WOODBURNE, Denver: When we saw Dr. Page's original report in the *Lancet*, we noted that he had demonstrated that patients with lupus erythematosus on quinacrine had shown an increase in the time for the minimum erythema dose of ultraviolet light from as much as 20 to 50%. We had had such good results in our cases of lupus erythematosus on quinacrine that we determined that this spring we would try quinacrine in our cases of solar dermatoses. We selected several older patients whom we had tried to handle during past seasons on various routines with only indifferent results. We chose several patients with hydroa aestivale, solar eczema, and solar urticaria, and were extremely pleased with the results we obtained. I sent a short report to the *A. M. A. Archives of Dermatology and Syphilology* shortly before leaving for this meeting in which, as I recall, there were 9 cases of hydroa aestivale and 10 or 12 of the other solar dermatoses, such as eczemas and urticarias. Everyone of the patients responded

satisfactorily and even more rapidly; all were able to stay out in the sun for much longer periods of time without the use of sun-screening agents, and the patients with the solar urticarias reported a loss of itching and burning within 24 hours.

DR. LAWRENCE G. BEINHAUER, Pittsburgh, Pa.: We have been very much interested in the treatment of this disease, especially the chronic hypertrophic discoid type similar to that shown in the uncolored photograph. Some years ago we tried to find a rationale for the curative results in this type when gold therapy was used. Drs. Traub and Monash reported good results when gold was injected into the local lesions. In our study with the spectrograph we were able to show the deposition of gold in healed lesions, whereas no gold was present in the unhealed lesions.

Dr. Kierland mentioned that quinacrine was injected into the lesions without response. In theory, vasodilation has been advanced as a means for promoting a freer deposition of the medication into the tissues. Our experience with orally administered vasodilators has not provided the answer. For this means we used locally a solution composed of equal parts of trichloracetic acid, alcohol, and phenol, applied to produce a local whiteness with a resultant local redness and subsequent vasodilation of the tissues. Orally, we used the technique of Dr. Kierland, but later, at the suggestion of Dr. Belisario of Sydney, we incorporated the use of vitamin B_{12}. This combination we found produced much better results, especially in the chronic hypertrophic discoid type.

Biweekly injections of B_{12}, 50 γ, were given, together with B_{12}, 25 γ, and quinacrine, 100 mg., orally each day for a period of two weeks. The quinacrine was then reduced to 50 mg. and continued for two weeks. A rest period of one month was followed by readministration of the medication.

In general our experience with this drug has been as Dr. Kierland reported, and we mention our experience with a modified treatment, especially in the hypertrophic discoid type for further trial.

I should like to ask Dr. Kierland to include in his closing remarks an experience he has had with vitamin B_{12} in this disease. We feel it has a synergistic action of some sort.

DR. MARION B. SULZBERGER, New York: I, too, want to add my congratulations to Drs. Kierland, Brunsting, and O'Leary for this very conservative, careful, and useful report. I think that all dermatologists who have had experience with quinacrine now agree with practically every finding they have mentioned. I might say that the report by Dr. Lewis and his group from Cornell and the report by Dr. Sawicky and his group from the Skin and Cancer Unit and the newly added cases from our group in New York make well over 200 cases of discoid lupus erythematosus that have been treated with quinacrine and then followed for varying periods. There has not been one divergent finding from those which you have just heard reported.

I should like to call attention to a paper, which is now in press and which I had the privilege of seeing, by George Harvey and Thomas Cochrane of Glasgow, on 62 cases of lupus erythematosus of the discoid type, treated with quinacrine and also with other drugs, other drugs of the flavine series; and some cases also with drugs of the quinone series, related to quinine. The results were uniformly negative with the quinone derivatives and quinine relatives. That, I think, shows that the mechanism is in all probability not related to the antiplasmodial effect; in other words, every good antimalarial is not necessarily also good against lupus erythematosus. In that report, there is also mention of four cases of subacute lupus erythematosus and one case of acute ("systemic") lupus erythematosus treated successfully with quinacrine. I should like to ask Dr. Kierland and his co-authors whether they used the same dose of quinacrine in the acute cases or systemic cases, as they call them, which they treated. I think it is possible that the dosage may be too high, that is, the dosage which is useful in chronic discoid lupus erythematosus may have to be much reduced in the early phases of treatment of the acute variety. We are now trying to treat some patients having the acute variety of the disease with as little as 50 mg. a day, but it is much too early for us to say anything final about the results.

I do think, however, that it is logical, if we all are of the opinion which I think most of us hold, namely, that discoid lupus erythematosus, subacute lupus erythematosus, and the acute disseminated variety are one and the same disease, not to give up too soon the attempts to try drugs of this flavine series also in the acute variety. Perhaps we should add all the other

measures at the same time, that is, those which have been found sometimes to be somewhat helpful in the acute variety (e. g. cortisone and corticotropin), while giving small doses of quinacrine.

As far as the mechanism is concerned, in addition to what I have said about it probably not being anything related to the antiplasmodial effect, I think that the idea of the reduction of photosensitivity is certainly one which merits the most attention to start with. A young man by the name of Rubin in our school noted that while he was in the Pacific, persons who were getting quinacrine continuously for the prophylaxis of malaria showed less tendency to skin damage from exposure to the sun. I think it would be worth while to study this systematically, and in a scientific fashion to study the possible elevation of threshold sensitivity to sunlight on the part of patients getting quinacrine.

Dr. Paul E. Bechet, Elizabeth, N. J.: I did not hear any of the speakers mention the duration of the yellowish to brownish discoloration of the skin following the use of quinacrine. Some of my patients have had it for months, after the cessation of use of quinacrine in the recommended dosage of 75 to 100 mg. daily for a month and 50 mg. a day for an additional month or two. As long as a year or two after World War II, I observed a few veterans from the Pacific area who after prolonged use of quinacrine in large doses for malaria showed marked discoloration of the skin; the color of one of them resembled that of a piebald horse. All of them had been taking quinacrine over a long period of time. That quinacrine can at times show better results than aurotherapy was proved in a woman with lupus erythematosus of the disseminated discoid type on the face, chest, arms, and hands, which started after a severe sunburn. The patient was in good health, and a number of differential blood counts proved normal. Under aurotherapy the lesions entirely disappeared. After a second severe sun exposure the lesions reappeared, but only on the face. This time aurotherapy proved useless, and quinacrine was given orally in doses of 100 mg. daily for a month, then 50 mg. daily for an additional month. Blood counts again proved normal. Yellowish discoloration became evident on the second week of atabrine therapy, but mostly on the exposed areas. It was still present several months later, but the lesions had practically disappeared.

Dr. Norman N. Epstein, San Francisco: I don't wish to prolong the discussion, because our experience has been quite the same as has been reported here, but I should like to report one observation that may be of some importance.

This patient, a woman, had had discoid lupus erythematosus rather extensively over her face, behind the ears, and over the upper back for several years. Her lesions disappeared quite promptly on the administration of quinacrine in the dosage recommended. However, while the face and exposed parts cleared completely in the usual length of time, I was rather surprised to find that the lesions on the back did not respond at all. This being a covered part of her body, I think it may be some evidence in favor of the theory that the action of quinacrine is related to photosensitivity.

Dr. E. J. Trow, Toronto, Canada: This paper has been interesting to me because one of my associates, Dr. Wrong, and my son, Dr. E. J. Trow, Jr., have been, I think, probably among the first, if not the first, on this continent to use quinacrine in the treatment of lupus erythematosus.

I want to make only one observation, and that is one that may be of some importance. I should like to ask Dr. Kierland whether he has had this experience. They had a case of vitiligo, with accompanying lupus erythematosus of the discoid type, and the staining did not penetrate the vitiliginous areas. It made rather a curious picture, and it would seem, then, that the quinacrine is deposited as is melanin.

Dr. Herbert S. Alden, Atlanta: Since this fascinating treatment for lupus erythematosus was dropped into our laps last year, we have had an opportunity to observe some 12 patients with lupus erythematosus, and the results have paralleled what Dr. Kierland has described. Of these 12 patients, however, there were only three males. It is very curious that all three of these males complained of loss of libido after taking quinacrine. I mention that as a form of reaction to the drug.

Dr. Louis A. Brunsting, Rochester, Minn. (Closing): The yellowing of the skin which occurs with quinacrine therapy is never a practical reason for objection to the use of the drug

when it seems indicated. Most patients with the disfigurement of chronic discoid lupus erythematosus are happy to participate in an experiment which will provide them with a considerable degree of relief and often clearing of their disease, and will pay no attention to the staining of the skin. The color may persist for three months or longer after quinacrine is discontinued. Fluorescence of the nails under the Wood lamp can be visualized for six months or longer.

The yellowing is intensified on the exposed skin of certain patients, especially redheads, and in areas of hyperpigmentation such as freckles. Dr. Trow noticed the absence of yellowing in sites of vitiligo.

Certain of these patients have had supplementary treatment in addition to quinacrine, when a preliminary trial of three to six months showed an inadequate response to the drug. Our unfavorable experiences have all occurred in patients who had systemic lupus erythematosus or were on the borderline. Special precautions should be taken in cases in which there are fever, leukopenia, considerable elevation of the sedimentation rate, positive Hargraves' phenomenon or nondescript symptoms which may be related to systemic involvement.

The notion that quinacrine may cause loss of libido or impotence was a familiar wartime rumor among military personnel in the Pacific. It has no foundation in fact, according to the experience of some of my professional colleagues who are in a position to speak authoritatively on the subject.

It is evident from the discussion today and from the reports in the literature that lupus erythematosus in both chronic and systemic forms is a common disease. No one can estimate its actual incidence. It might be well to establish a central registry on a national basis for the recording of such patients for group and statistical surveys, much as is done in the case of bone sarcomas, and so forth. At the present time I do not know how such a registration could be practically accomplished.

SUPERFICIAL FUNGUS INFECTIONS IN INFANTS

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DETROIT

IT IS WELL known that superficial infections caused by the Candida species (intertrigo, glossitis, perlèche, etc.) are relatively common in infants. Also, tinea favosa (a rare fungus infection of the scalp) tends to involve more than one member of the family, including infants. With the exception of these two forms of dermatomycosis, the modern textbooks of dermatology and pediatrics do not mention tinea infections occurring in infancy. However, Duhring,[1] in his textbook on diseases of

TABLE 1.—*Data on Eleven Reported Cases of Superficial Fungus Infections in Infants*

Authors	Case No.	Age	Areas of Infection	Causative Organism
White (1927) [3a]	2	Both 18 mo.	Not recorded	Not recorded
Pignot and Photinos (1929) [3b]	1	4 mo.	Generalized	Epidermophyton floccosum
Milian (1929) [3c]	1	3 mo.	Genitocrural	Not recorded
Peck and Salomon (1931) [3d]	1	4 mo.	Generalized	Not recorded
Weidman (1934) [3e]	2	Both 18 mo.	Not recorded	Not recorded
Petges and Lecoulant (1937) [3f]	1	12 mo.	Scalp and trunk	Trichophyton ferrugineum
de Castro (1945) [3g]	1	17 days	Face and head	Not recorded
Meinert (1949) [3h]	2	3 mo. 4 mo.	Generalized	Trichophyton gypseum

the skin, published in 1888, stated that infants are very susceptible to ringworm infections. He cited a case which had been reported by Lynch [2] in 1876; in this instance a lesion, noted six hours after birth, was identified as tinea circinata when the child reached 3 weeks of age.

During the past year we have observed 10 infants who had superficial fungus infections. In each instance the disease had its onset before the age of 12 months. We believe that a brief summary of these cases and a review of the literature on this subject will be of general interest, inasmuch as there are so few recorded observations on the occurrence of this disease in babies.

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1. Duhring, L. A.: Diseases of the Skin, Ed. 3, Philadelphia, J. B. Lippincott Company, 1888, page 605.

2. Lynch, J. R.: Case of Ringworm in an Infant Within Six Hours of Birth, Med. Press & Circ. **21**:235 (March) 1876.

Table 1 gives the pertinent data on 11 cases which have been recorded in the literature during the past two decades.[3] Doubtless other references to dermatophyte fungus infections in infants are buried in society transactions and in discussions of papers dealing with superficial mycotic infections in general.

Similar data in regard to our 10 cases are summarized in Table 2.

COMMENT

All the infants in this series, with the exception of one patient (D. Z.), had an uneventful recovery after treatment with topical antifungal preparations. Each patient was discharged as cured within two to six weeks after treatment was initiated. The course of this disease was not different from that of similar infections

TABLE 2.—*Superficial Fungus Infections in Infants*

No.	Name	Approximate Age of Onset	Race	Sex	Clinical Diagnosis	KOH Mount	Culture
1	D. Z.*	3 wk.	W	M	Tinea capitis	Pos.	Microsporum lanosum
					Tinea corporis	Pos.	Trichophyton ferrugineum
2	M. E.	3 wk.	N	M	Tinea versicolor	Pos.	.....
3	A. H.	6 wk.	W	M	Tinea corporis	Pos.	Microsporum gypseum
4	B. M.	8 wk.	N	F	Tinea corporis	Pos.	No growth
5	D. W.	8 wk.	N	F	Tinea corporis	Pos.	No growth
6	T. W.	8 wk.	N	M	Tinea corporis	Pos.	Epidermophyton floccosum
7	R. T.†	5 mo.	N	M	Tinea cruris	Pos.	Epidermophyton floccosum
8	E. T.	7 mo.	N	M	Tinea capitis	Pos.	Microsporum lanosum
9	S. T.	7 mo.	N	M	Tinea corporis	Pos.	Microsporum lanosum
10	M. H.‡	12 mo.	W	M	Tinea pedis	Pos.	Trichophyton rubrum

* Figure 2.
† Figure 1.
‡ It is probable that the source of infection in this patient was the child's father, who was found to have tinea cruris due to T. rubrum. The source of infection in the other cases could not be determined. There was a history of contact with household pets in all patients with M. lanosum infections; however, these animals were not investigated as to a possible source of infection.

in adults with the exception of the infant with tinea pedis, due to Trichophyton rubrum. This infection cleared much more rapidly in the infants than it usually does in older patients.

3. (*a*) White, C. J.: Fungus Diseases of the Skin: Clinical Aspects and Treatment, Arch. Dermat. & Syph. **15**:387-414 (April) 1927. (*b*) Pignot, M., and Photinos, P.: Generalized Case of Epidermophytosis Due to Epidermophyton Inguinalis in 4-Month-Old Infant, Bull. Soc. franç. dermat. et syph. **36**:1075-1078 (Nov.) 1929. (*c*) Milian, M.: Case Reported in discussion on Pignot and Photinos.[3b] (*d*) Peck, S. U., and Salomon, G.: Eczema Due to Fungi: Case in 18 Months Old Baby, Arch. Dermat. & Syph. **24**:554-556 (Oct.) 1931. (*e*) Weidman, F. D.: Dermatophytosis Down to Date, Nebraska M. J. **19**:309-313 (Aug.) 1934. (*f*) Petges, G., and Lecoulant, P.: Ringworm in Infant 22 Months Old, Contracted in Region of Lake Tchad in Africa: Attempts at Indentification of Causative Parasite Which Resembles Trichophyton and Microsporon Ferruginosa of Ota, Ann. dermat. et syph. **8**:447-457 (June) 1937. (*g*) de Castro, C.: Herpes Circinatus in Newborn Infant, Hospital, Rio de Janeiro **28**:465-470 (Sept.) 1945. (*h*) Meinert, R.: Trichophytosis in Infancy, Monatsschr. Kinderh. **97**:252-256 1949.

The infant identified as D. Z. in Table 2 had postmeasles encephalitis, and possibly this chronic illness accounted for the unusual and severe manifestation observed in this case. The patient had an extensive tinea capitis due to Microsporum lanosum

Fig. 1.—R. T. Tinea cruris due to Epidermophyton floccosum. The angle at which this photograph was taken makes this 5-month-old baby appear to have an abnormally large penis.

Fig. 2.—D. Z. Tinea capitis due to Microsporum lanosum; Tinea corporis due to Trichophyton ferrugineum.

(isolated repeatedly). Also, he had large plaques of tinea corporis, which involved at least one-half of the glabrous skin areas. The causative organism was found to be Trichophyton ferrugineum. In addition, on numerous occasions Candida albicans

was cultured from erythematous moist crusted plaques on the infant's face. This case will be the subject of a separate detailed report, to be published at a later date.

An analysis of these cases, although of no real statistical significance, indicates a high incidence in the Negro infant and in the male infant. Only one of these patients was seen in private practice; the rest were observed in the dermatology section of the outpatient clinic or in consultation with the inpatient service of the pediatric department. It is possible that this apparent high incidence of superficial dermatophyte infection in infants of this area can be explained by the high temperature and humidity of this semitropical locality. A larger percentage of cases were seen during the late summer months.

SUMMARY

A review of the literature in tabular form of the cases of superficial dermatomycoses in infants and a report of 10 cases encountered in our experience during one year are presented. This type of infection in infants occurs more frequently than the dermatological literature on the subject would lead one to believe.

IMPROVEMENT IN TECHNIQUE OF DOPA REACTION

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IN A SERIES [1] of experiments it has been possible to demonstrate that the dopa reaction, which indicates the pigment-forming ability of melanocytes, may be clearly divided into two phases: (1) the spontaneous auto-oxidation of dopa solutions in a slightly alkaline medium without the action of an enzyme, and (2) the actual dopa reaction, which also takes place even more clearly and selectively in an acid medium.

It is known also that the dopa reaction occurs, nonspecifically, in the cells of the myeloid granular series (leucocytes, myelocytes).

The two reactions which may be obtained with dopa, the one with melanocytes and the other with granular leucocytes, show certain essential differences. The reaction in melanocytes varies according to the activity of the cell; it is relatively slow, inhibited by cyanides. It is apparently specific for dopa and for oxytyramine. It should be noted that Fitzpatrick and others [2] have obtained with an entirely original technique a similar reaction also with tyrosine; a fact which leads them to postulate the presence of a tyrosinase capable of forming dopa from tyrosine. This occurs only in skin irradiated with ultraviolet rays. Conversely, the reaction in leucocytes occurs more rapidly. It is always present and not inhibited by cyanides. It is undoubtedly nonspecific, since it may be obtained not only with dopa and oxytyramine, but also with epinephrine and with many other auto-oxidizable derivatives of benzene.

The usual procedure for the dopa reaction is based, as it is known, on the immersion of frozen sections, fixed in 5‰ formalin, in a 0.1% dopa solution, buffered to a slightly alkaline (ph 7.4) solution with phosphate buffer solutions.

With these methods [3] good results may be obtained both at room temperature and at 37 C., as long as the procedure of the reaction is very carefully controlled, in order to prevent nonspecific staining which will darken the whole section. This nonspecific staining occurs chiefly in the stratum corneum (especially adjacent to the stratum lucidum), the sweat glands, inflammatory infiltrates, etc. These phe-

From the Dermatological Clinic, University of Genoa, Prof. G. Mariani, Director.

1. Radaeli, G.: Ricerche sulla dopa-reazione di B. Bloch, Boll. Soc. ital. Biol. sper. **27**:707-716 (May) 1951; Ricerche e considerazioni sulla pigmento-genesi con particolare riguardo al meccanismo ed alla teoria della dopa-reazione di Bloch, Accad. med. **67**:111-129 (March) 1952.

2. Fitzpatrick, T. B.; Becker, S. W., Jr.; Lerner, A. B., and Montgomery, H.: Tyrosinase in Human Skin: Demonstration of Its Presence and of Its Role in Human Melanin Formation, Science **112**:223-225 (Aug. 25) 1950.

3. Bloch, B., in Jadassohn, J.: Handbuch der Haut-und Geschlechtskrankheiten, Berlin, Springer-Verlag, 1927, Vol. 1; 1929, Vol. 2. Glick, D.: Techniques of Histo- and Cyto-Chemistry, New York, Interscience Publishers, Inc., 1949.

nomena appear to be due to dopa melanin (which forms during the reaction in an alkaline medium), which has undoubted coloring capacities, which have noth-

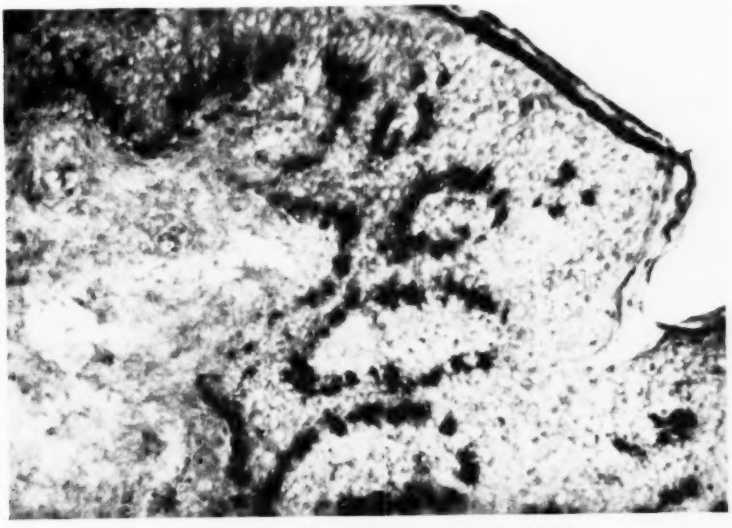

Fig. 1.—Normal prepuce-skin reaction at pH 7.2.

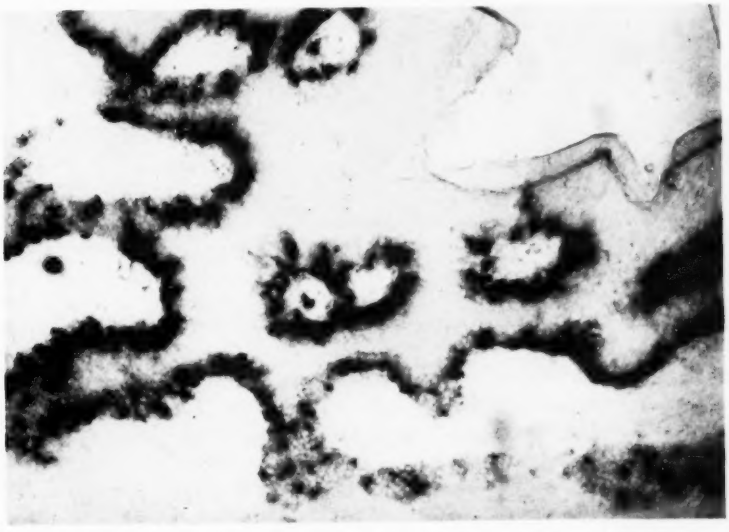

Fig. 2.—The same skin used for the reaction of Fig. 1. Dopa reaction at pH 6.2. Low-power view.

ing to do with the enzymatic oxidation of dopa. To avoid, at least partially, such phenomena, Laidlaw suggests that the solution be changed after the first 30 minutes of the reaction.

The experiments reported here have succeeded in preventing the nonspecific oxidation of dopa and overstaining of the section. It has been possible to demonstrate that the dopa reaction occurs in a slightly acid medium, in which dopa autooxidizes very slowly. All this, provided one allows the dopa solution to autooxidize itself very slightly, at pH 7.3 and 37 C., before transferring in it the frozen sections. The technique is presented below. Results are shown in Figures 1, 2, and 3.

REAGENTS AND MATERIALS

1. Doubly distilled water
2. Dopa (1-dihydroxyphenylalanine)
3. A vacuum flask, with stopper, of the capacity of about 150 ml., airtight when anointed with petrolatum

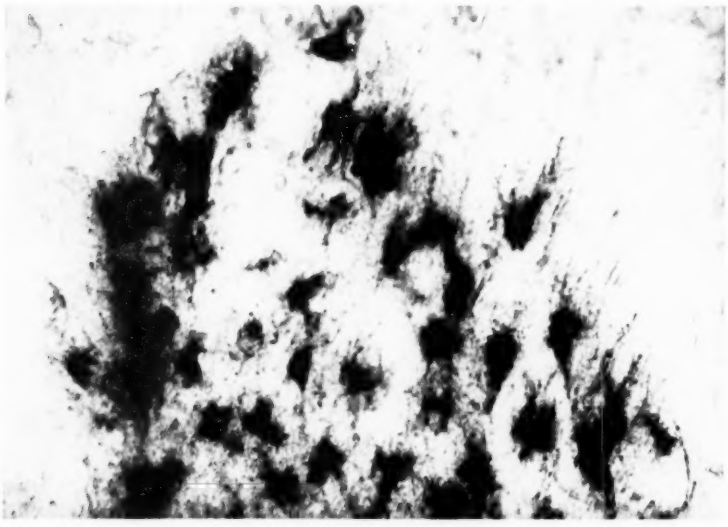

Fig. 3.—Section of Fig. 2. High-power view.

4. A certain number of small glass tubes
5. 100 ml. of a M/15 solution of monopotassium phosphate: 0.908 gm. in 100 ml. of previously boiled doubly distilled water
6. 100 ml. of M/15 disodium phosphate solution, 1.188 gm. in 100 ml. of water as above
7. An efficient vacuum oil pump

The 0.1% dopa solution is prepared in the airtight flask as follows: 100 ml. of distilled water are brought to boiling point for a few minutes at room temperature in the vacuum; the flask is opened, and 0.1 gm. of dopa is added. The flask is closed, and vacuum is created again. This slightly acid and air-free solution may be kept unaltered and ready for use for months. Each time the necessary quantity of dopa solution is withdrawn, vacuum should be immediately reestablished. Should the solution turn brown, it would mean that the vacuum has not maintained itself or was insufficient; the solution should be accordingly changed. Rubber stoppers should not be used for this flask.

The dopa solution may be prepared for each experiment and immediately used; however, such a procedure is less practical.

TECHNICAL PROCEDURE

Ten milliliters of the 0.1% dopa solution is placed in a large test tube; 2.5 ml. of the disodium phosphate solution is added. This results in a buffered solution of pH 7.2 to 7.3. Three small test tubes are then prepared, in each of which 2.5 ml. of the alkalinized dopa solution is placed. Tubes 1 and 2 are placed for 45 minutes in a water bath at 37 C. During this period the slightly alkaline dopa solution becomes slightly oxidized, assuming a barely perceptible brownish-pink hue. After the tubes are removed from the water bath, they are acidified by addition of 0.6 ml. of monopotassium phosphate solution to Tube 1 and 1.2 ml. of the same to Tube 2; the two solutions are changed to pH 6.5 and pH 6.2.

Skin or other material should be fixed for one hour in 5‰ formalin. In all three tubes four or five frozen sections are placed, from distilled water, to be stained. Tube 3 serves as a control and will give the result of the dopa reaction in a slightly alkaline medium; there is, however, the advantage that also this last dopa solution contains very little oxygen.

Tubes are allowed to remain at room temperature for about 18 to 20 hours; this period, even if prolonged, has very little influence on the results of tests in Tubes 1 and 2, preoxidized at 37 C. and subsequently acidified. As a matter of fact, in these tubes the dopa solution turns very slightly brown and loses its pinkish hue, but does not blacken. Tube 3 solution has instead a tendency to blacken, and the course of the reaction on sections should be frequently examined under a microscope. However, with thin tubes such as those mentioned being used and with a preventively deacrized solution having been employed, results are almost always superior to those obtainable with ordinary methods.

After some 20 hours of treatment, sections are transferred in distilled water. They are subsequently carefully isolated on a glass slip, dried with blotting paper, and allowed to dry further in the air; then they are dehydrated in alcohol and xylene and mounted in balsam.

It will be noticed that the sections in which the reaction has taken place in the more acid medium (Tube 2) will show the greatest selectivity of the reaction itself. There is no non-specific staining of the section, and only the active melanocytes and granulocytes which may be present show new black deposition. The dendritic processes of the epidermal melanocytes are easily traced on the clear background of the preparation.

The section from Tube 1, pH 6.5, shows occasionally a more intense reaction, which of course does not contribute to the greater selectivity of the staining. Sections of Tube 3 (alkaline) contain a diffuse brown color. These latter sections are therefore sometimes more difficult to interpret, while the intensity of the reaction in the melanocytes proper is no greater than in the acidified tubes.

It should be mentioned that in Tubes 1 and 2, preoxidized and then acidified, the reaction in granulocytes develops much more quickly than in melanocytes.

SUMMARY

A new method for performing the dopa reaction is proposed. By this technique the reaction may be obtained in a slighly acid (pH 6.2 to 6.5) instead of basic (pH 7.4) medium as done usually. It is thus possible to obtain less overstaining, and the reaction is accordingly more selective.

METABOLIC CALCINOSIS IN THE NEWBORN

Report of a Case

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CASES of cutaneous calcinosis have been described in the literature often enough so that they can by no means be considered rare. However, calcinosis in a newborn infant has been seen on relatively few occasions. Accordingly, our recent observations concerning an infant whose illness began at the age of 2 weeks seemed worthy of publication. Before presenting the report of our case, we shall summarize the important features of the disease as they have been recorded in the literature.

CLASSIFICATION

Maloney and Bloom [1] divided calcinosis into local and general types, the former being a purely local disease denoting calcification in tumors, cysts, and hematomas, and the latter resulting from a widespread disturbance within the body. The etiologic classification presented by Peters and co-workers [2] divided the cases into four categories: (1) those in which the calcification results from known disturbances of calcium or phosphorus metabolism; (2) those in which calcification occurs locally in cysts, hematomas, and abscesses; (3) those in which the calcification is associated with cutaneous disturbances, such as scleroderma, dermatomyositis, and Raynaud's disease, and (4) those in which no cause is apparent.

Perhaps most commonly, the disorder has been divided into three main groups: calcinosis circumscripta, calcinosis universalis, and metastatic calcification. However, it has been pointed out [3] that differentiation between calcinosis circumscripta and calcinosis universalis is frequently difficult and that the separation may be an artificial division of what are actually different stages in the degree of development of the same process.

The term metabolic calcification, denoting calcinosis resulting from some unknown disturbance of calcium and phosphorus metabolism, has been used by various authors to include both of these forms. We feel that for the sake of sim-

1. Maloney, E. R., and Bloom, D.: Cutaneous Calcinosis: Report of Case, Arch. Dermat. & Syph. **23**:245 (Feb.) 1931.

2. Peters, J. H.; Horn, R. H., and Greeman, L.: Idiopathic Calcinosis Universalis Cutis Without Disability, Ann. Int. Med. **32**:138 (Jan.) 1950.

3. (*a*) Nunez, B. E., and Arthur, P. S.: Calcinosis: Report of 2 Cases, M. Ann. District of Columbia **12**:301 (Aug.) 1943. (*b*) Rothstein, J. L., and Welt, S.: Calcinosis Universalis and Calcinosis Circumscripta in Infancy and in Childhood: 3 Cases of Calcinosis Universalis, with Review of Literature, Am. J. Dis. Child. **52**:368 (Aug.) 1936.

plicity, one might divide a general heading of calcinosis into the two main subgroups of calcinosis cutis and metastatic calcinosis. The former could, in turn, be subdivided into the local type, denoting calcification in cysts and tumors, and the general type, this being further divided into metabolic calcinosis and calcinosis in which calcification is associated with systemic diseases, such as scleroderma. It is recognized that such a classification is not complete, since arterial calcification, urolithiasis, and presence of concretions in the biliary, salivary, and pancreatic ducts and of stones in the bronchi and lungs are not included.

In the following review, we shall be concerned exclusively with calcinosis cutis of the metabolic type, since in the case to be reported the condition was diagnosed as such.

ETIOLOGY

Many theories concerning the etiology of metabolic calcinosis have been propounded, but there is none which has been universally accepted. The greater frequency of calcinosis in the female has supported the concept of an endocrinologic basis. Hypercholesteremia was considered a cause by Moggi,[4] but abnormal values for cholesterol have not been found in other patients. In all cases, with the exception of those reported by Hein,[5] Tyson and Weiss,[6] Staub,[7] and Costello,[8] normal blood levels of calcium and phosphorus have been found. Thannhauser [9] discarded the idea of a generalized disturbance of calcium metabolism and considered calcinosis an expression of locally damaged tissue. Tisdall and Erb [10] found the calcareous deposits in sites of previous degenerative change. In some reports trauma and infection have been emphasized as precursors of calcinosis. Tissue change secondary to disturbances of the vascular supply to a part has been suggested as a factor predisposing to the deposition of calcium salts. Morse [11] postulated a primary degeneration of fat, possibly due to a lipolytic ferment in the subcutaneous tissue, and Weidman and Shaffer [12] concluded from the study of their case that the calcification followed a disturbance of fat metabolism in the epidermal cells, the deposition occurring secondary to the fatty degeneration. Bauer and co-workers,[13] as a result of calcium and phosphorus balance studies, concluded that there is a marked tendency for the tissues to retain absorbed calcium and phosphorus, in spite of normal blood levels for these substances. The histologic study they conducted revealed no evidence of antecedent tissue necrosis and led to their belief that the increased retention of calcium and phosphorus is the result of an as yet undetermined local cellular condition.

4. Moggi, D., cited by Rothstein and Welt.[39]

5. Hein, B. J.: Calcinosis Universalis, Arch. Surg. **26**:389 (March) 1933.

6. Tyson, R. M., and Weiss, S.: Calcinosis Interstitialis Universalis: Report of Case with Improvement, Arch. Pediat. **53**:550 (Aug.) 1936.

7. Staub, V., cited by Barr, D. P.: Pathological Calcification, Physiol. Rev. **12**:593 (Oct.) 1932.

8. Costello, M. J.: Cutaneous Calcinosis, New York J. Med. **35**:1206 (Dec. 15) 1935.

9. Thannhauser, S. J., cited by Barr, D. P.: Pathological Calcification, Physiol. Rev. **12**:593 (Oct.) 1932.

10. Tisdall, F. F., and Erb, I. H.: Report of 2 Cases with Unusual Calcareous Deposits, Am. J. Dis. Child. **27**:28 (Jan.) 1924.

11. Morse, J. L.: Calcification of Skin in Child, Am. J. Dis. Child. **22**:412 (Oct.) 1921.

12. Weidman, F. D., and Shaffer, L. W.: Calcification of the Skin, Including the Epiderm in Connection with Extensive Bone Resorption, Arch. Dermat. & Syph. **14**:503 (Nov.) 1926.

13. Bauer, W.; Marble, A., and Bennett, G. A.: Further Studies in Case of Calcification of Subcutaneous Tissue ("Calcinosis Universalis") in Child, Am. J. M. Sc. **182**:237 (Aug.) 1931.

AGE

Of 105 cases of calcinosis gathered by Steinitz [14] in 1931 from the literature, 71 were classified as instances of calcinosis circumscripta and 34 of calcinosis universalis. A significant observation was that the youngest patient with calcinosis circumscripta was 4 years of age and the oldest 82, while the youngest patient with calcinosis universalis was 5 weeks of age and the oldest 36 years.

Rothstein and Welt [3b] in 1936 found reports in the literature of 36 cases of metabolic calcinosis in infants and children up to the age of 13 years, and to these they added 3 of their own. Of the 39 cases, the condition occurred in 3 within the first two months of life. One of these, reported by Zarfl, was that of a 7-week-old infant whose symptoms of weakness, areas of pigmentation and tightening of the skin, and presence of hard palpable nodules began at the age of 10 days. The second was Case 1 of Tisdall and Erb,[15] that of a 5-week-old child who since birth had shown marked emaciation and weakness and flexion deformity of almost all joints, with secondary contracture of muscles. The third was that of the patient of Forster and Swanson,[15] in whom hard subcutaneous nodules developed at the age of 6 weeks, the nodules beginning at the knees and extending up the thighs to include the buttocks and laterally to the iliac crests. Rothstein and Welt [3b] also cited the case of the 7-week-old boy presented at a pediatric meeting by Goldreich, but they did not include it in their series because a description of the findings and history were not published. Bloxsom and Johnston [16] in 1938 reported on a newborn infant who at birth showed deposits of calcium in the epiphyses of the long bones and about the vertebrae and other bones in association with generalized hyperkeratotic thickening of the skin.

SEX

Among the cases of calcinosis circumscripta in Steinitz' series,[14] there was a female to male ratio of almost 6:1, whereas in the cases of calcinosis universalis there was about an equal sex distribution.

Rothstein and Welt [3b] had seven cases of calcinosis circumscripta among their series of children, five of whom were girls and two were boys, or a ratio of 2.5:1. Of their 32 cases of calcinosis universalis, the corresponding ratio was 1.7:1. As they pointed out, the female to male ratio for the total number of cases in children was 1.8:1, in contrast to the ratio of 5.7:1 for all age groups in Steinitz' series.

Among the four reported cases of calcinosis with onset during the first two months of life, three of the patients were girls and one was a boy.

CLINICAL PICTURE

Characteristic of metabolic calcinosis is the finding of hard nodules and plaques. In calcinosis circumscripta the deposits occur in the skin and subcutaneous tissue, while in calcinosis universalis they are found not only there but also in nerve, tendon, and muscle. The tumors vary considerably in size, and in the so-called circumscript

14. Steinitz, H., cited by Rothstein and Welt.[3b]

15. Swanson, W. W.; Forster, W. G., and Ioh, L. V.: Calcinosis Circumscripta, Am. J. Dis. Child. **45**:590 (March) 1933.

16. Bloxsom, A., and Johnston, R. A.: Calcinosis Universalis with Unusual Features, Am. J. Dis. Child. **56**:103 (July) 1938.

type they are most commonly found symmetrically distributed over the extremities, particularly on the fingers and toes, whereas in the universal form the calcification is more widespread, with infrequent involvement of the fingers and toes and commoner localization about the pelvis and the larger joints. The nodules are generally painless at the beginning, with the overlying skin freely movable and of normal appearance. Later the masses may become painful and tender, and the overlying skin may redden and ulcerate, with the discharge of a material which has been described as chalk-like, creamy, and pus-like. According to Epstein,[17] such a discharge occurs in half the cases. Analysis of the material [1] has repeatedly demonstrated the presence of a great quantity of calcium phosphate and a small amount of calcium carbonate. After the breakdown of the mass, it decreases in size, but a sinus tract, which heals with difficulty, often remains.

Symptoms depend to a large extent upon the location of the calcareous deposits. Those on the tips of the fingers more commonly are painful and tender, while in other locations there may be limitation of motion due to stiffening of the skin and muscles and pain may arise from pressure of the masses when sitting or lying. In some instances, infection may occur after ulceration, and this, particularly in infants and children, presents the danger of sepsis.

Roentgenographic studies are of great value in confirming the diagnosis of calcinosis. In the x-ray picture the calcific deposits appear as dense shadows of varying size and shape. Of significance is the fact that x-ray examination may reveal calcium deposits which are too deep to be palpated. This was demonstrated in Tisdall and Erb's first case,[10] in which there was no involvement of soft tissue, the calcific deposits being limited to the epiphyses of the long bones and to the patellae. Similarly, in Bloxsom and Johnston's case,[16] the masses were not palpable but x-rays revealed extensive deposits of calcium.

HISTOPATHOLOGY

Although the epidermis and upper corium may be involved in metabolic calcinosis, it is the subcutaneous tissue and deeper portion of the corium which are generally the sites of calcific deposits. The characteristic changes have been described by Bauer, Marble, and Bennett.[13] They noted that the earliest abnormality was the deposition of finely divided calcium particles around the periphery of fat cells which otherwise histologically appeared normal. They observed what appeared to be progression of the disease process until calcium had been deposited within the fat cells and eventually replaced whole fat lobules. The calcium deposits then acted as foreign bodies and stimulated fibrosis, the formation of giant cells, and lymphoid cell infiltration. They also noted that some nodules had fused into large masses, some of which had broken down and partially extruded their contents.

TREATMENT AND PROGNOSIS

Despite numerous therapeutic approaches, there is as yet no specific treatment for calcinosis. Physical therapy, surgery, and glandular extracts, such as parathyroid extracts, acetylcholine, insulin, and salts of pilocarpine have been used unsuccessfully.

17. Epstein, E.: Idiopathic Calcinosis Cutis: A Review, with a Report of 2 Cases, Arch. Dermat. & Syph. **34**:367 (Sept.) 1936.

Craig and Lyall,[18] Tyson and Weiss,[6] and Brooks [19] noted a marked improvement in their cases following oral therapy with disodium hydrogen phosphate. On the other hand, Jacobowitz [20] and Rothstein and Welt [3b] were unsuccessful in their cases in which this form of treatment was used. The use of a ketogenic diet was advocated by Kennedy,[21] but his results have not been confirmed by others. Bauer, Marble, and Bennett [13] observed some improvement in their patient treated with ammonium chloride and a low-calcium diet. Heliotherapy was recommended by Hein.[5]

The course of metabolic calcinosis tends to be chronic, with remissions and exacerbations. Improvement and, in some cases, complete disappearance of nodules has occasionally been noted. In general, the outlook for long life is excellent.

Of the four cases of metabolic calcinosis occurring within the first two months of life, in the ones reported by Zarfl [22] and by Swanson and co-workers [15] the patients completely recovered without treatment; in that of Bloxsom and Johnston [16] there was a spontaneous tendency toward diminution of the deposits, while in Case 1 of Tisdall and Erb [10] the patient died one month after the onset of illness.

REPORT OF CASE

A white boy 2 months old, weighing 8 lb. 4 oz. (3,740 gm.), was admitted to Pawtucket Memorial Hospital on July 24, 1951, presenting widespread "nodular lesions."[23]

The mother, aged 22, was of Irish-American extraction, and the infant was the product of her first pregnancy. Her history was essentially normal. The father was 23 years of age and in good health. The history revealed no incidence on either side of the family of such a condition as is herein reported.

The child was delivered on May 16, 1951, after a long difficult labor, necessitating midforceps application. At the time of birth physical examination disclosed no abnormalities.

The mother stated that about three weeks after his birth she noticed "hard lumps" on the infant's cheeks and chest. The baby ate poorly, vomited about every third day, and failed to gain weight. The pediatrician was consulted on July 1, 1951, and hospitalization was advised.

The patient was first seen by one of us (B. L. S.) on July 24, 1951. Examination revealed a fairly well-developed white male infant who showed no obvious abnormalities except for the following findings: The skin had a yellowish-gray tinge and was dry. On attempts to lift the baby, rigidity was noted, and at times he assumed a bizarre position with his right arm extended in "boxer" fashion (Fig. 1). He appeared to keep the extremities in a state of flexion. Attempts to further flex forearms on arms and legs on thighs were met with resistance.

On palpation, hard nodules and plaques, varying in diameter from 2 to 6 cm., were felt on the cheeks, mandibles, neck, thorax, and upper and lower extremities. The hands, feet, and abdomen were not involved.

The lesions were located in the subcutaneous tissues and were freely movable over the deeper structures. The regions primarily affected were the back of the neck, cheeks, and extremities. Involvement of the cheeks and thighs was so extensive as to occupy almost all of those regions (Figs. 2 and 3). The skin overlying the nodules and plaques showed no inflammatory process, and no tenderness was elicited by pressure.

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18. Craig, J., and Lyall, A.: A Case of Calcinosis Universalis, and a Suggested Method of Treatment, Brit. J. Child. Dis. **28**:29 (Jan.-March) 1931.

19. Brooks, W. D. W.: Calcinosis, Quart. J. Med. **3**:293 (July) 1934.

20. Jacobowitz, H., cited by Rothstein and Welt.[3b]

21. Kennedy, R. L. J.: Calcinosis: Case, Proc. Staff Meet., Mayo Clin. **7**:329 (June 8) 1932.

22. Zarfl, M., cited by Rothstein and Welt.[3b]

23. This case was referred to us for study by Dr. Joseph Doll, of the Pediatric Department, Pawtucket Memorial Hospital.

Fig. 1.—Flexion position of the extremities due to the calcific deposits in the soft tissues.

Fig. 2.—Large subcutaneous mass occupying almost all left cheek.

Fig. 3.—Large subcutaneous mass in thigh as outlined by fingers.

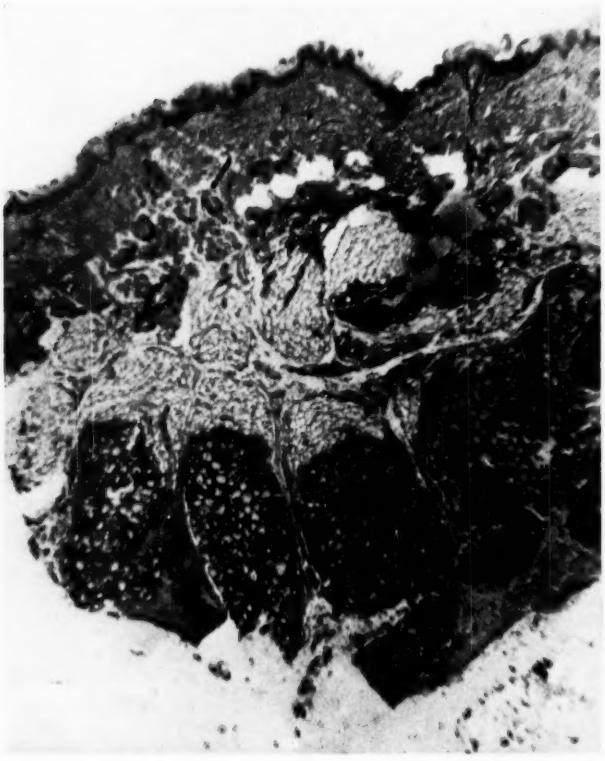

Fig. 4.—Photomicrograph (low power) showing extensive calcium deposits in subcutaneous tissue.

Laboratory Studies.—Serologic tests for syphilis were negative. The peripheral blood showed an erythrocyte count of 3,160,000 per cubic millimeter, a white cell count of 14,700, with 80% neutrophiles, 11% lymphocytes, 5% eosinophiles, and 2% polychromatophilic cells. The amount of hemoglobin was 8.2 gm. per 100 cc. Urinalyses gave normal values, and Sulkowitch test for calcium in the urine was negative. Chemical studies of the blood revealed 5.8 mg. of phosphorus, 8.7 mg. of calcium, and 302 mg. of serum cholesterol per 100 cc.; the alkaline phosphatase activity was 2.8 units (Bodansky).

Histopathology.—One biopsy specimen was taken from each thigh, the first on Aug. 1 and the second on Sept. 2, 1951. The microscopic changes (Fig. 4) were described by Dr. Herbert Fanger, Director of the Institute of Pathology, Rhode Island Hospital. The epidermis was intact and showed mild hyperkeratosis. The skin appendages were present in average quantity. The immediately underlying adipose tissue showed nodular focal areas of calcification. In these calcific nodules, the outline of the capsule was fairly well maintained, the deposit of calcium

Fig. 5.—Roentgenogram showing widespread calcification of soft tissues.

being at the periphery. In some areas there was a visible cellular reaction, these cells being of spindle type, round or ovoid in configuration. The nuclei had a coarse reticulum and a faint nucleolus. An occasional multinucleated giant cell could be found in these aggregations. These cells faded off imperceptibly into fibroblastic type cells at the periphery of the nodular masses. The diagnosis was calcinosis universalis.

Roentgenologic Examination (Dr. R. Rosin) (Fig. 5).—On Aug. 3, 1951, the head, neck, thorax, abdomen, and upper and lower extremities showed extensive calcium deposits of mottled character and without any definite structure, in all the subcutaneous tissues except those overlying the calvarium, the abdomen, and the hands and feet. The most extensive deposits were present in the subcutaneous tissues of the neck and the upper thorax, posteriorly. Studies of the chest contents revealed no evidence of calcium deposits. Reexamination on Sept. 24 disclosed no apparent change in degree of subcutaneous calcification, except that the soft tissues of the abdominal wall showed calcification similar to but less extensive than that seen elsewhere in the body.

The infant's temperature remained higher than normal, and he continued to vomit. He was given several transfusions and hypodermoclyses. On Aug. 4, cortisone therapy was instituted, 15 mg. being given every six hours. Under this treatment, the patient took nourishment well but failed to gain weight. This therapy was continued until Sept. 15, with no improvement in the skin lesions. The patient was discharged from the hospital at the parents' request on Sept. 15.

However, on Sept. 20 the patient was readmitted because of continued vomiting, elevated temperature, and dehydration. At this time, new masses could be palpated in the abdominal wall. He was given several transfusions and additional symptomatic treatment. He failed to respond; bronchopneumonia developed, and he died on Oct. 4. Permission for postmortem examination was refused.

SUMMARY

A review of the literature concerning metabolic calcinosis is presented, and a simple classification is suggested.

A case of metabolic calcinosis in a newborn, with fatal termination, is reported.

251 Broadway.

247 Waterman St.

ETIOLOGY OF SUPERFICIAL MYCOSES IN MIDWESTERN UNITED STATES

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THIS paper presents a compilation and brief discussion of superficial mycoses observed in three widely separated areas of the midwestern United States. It will be noted that the incidence of infection with the various dermatophytes is not the same as in other reported studies.

During the period between July, 1949, and May, 1952, a total of 674 cases were observed. In each case the etiologic organism was cultured. These cases were seen in the Barnard Free Skin and Cancer Hospital, St. Louis, and in offices in Springfield, Mo., and Oklahoma City.

MICROSPORUM AUDOUINI

Of the 115 cases of infection with M. audouini 107 were reported from St. Louis. This disproportion cannot be easily explained, except that it may be said that the widespread epidemic of infections due to this organism did not extend into the southwestern states. In Springfield, Mo., the only cases of infection with M. audouini were in children who had recently come from epidemic areas and who had clear histories of lesions having developed while they were there. Lewis and Hopper [1] have noted that infections with M. audouini and M. canis are equally frequent in the eastern United States, that M. audouini infections are more frequent in the Midwest, and that M. canis infections are more frequent in the South and Southwest. This is not strictly true in our series and is not in agreement with a report from Philadelphia,[2] where M. audouini infections greatly predominated. In the St. Louis area it is felt that M. audouini is still causing disease of epidemic proportions but below the peak years of 1942 to 1944.[3]

From the Division of Dermatology, Washington University School of Medicine and the Barnard Free Skin and Cancer Hospital (Dr. Sisk); the St. John's Hospital (Dr. Wooldridge), and the office of Dr. Lain, Dr. Lamb, Dr. Jones, and Mr. Rollin Koons, Mycologist (Dr. Lamb).

1. Lewis, G., and Hopper, M.: An Introduction to Medical Mycology, Ed. 2, Chicago, Year-book Publishers, Inc., 1943, pp. 47-48.

2. Livinggood, C. S., and Pillsbury, D. M.: Ringworm of the Scalp: Prolonged Observation, Family Investigation, Cultural and Immunologic Studies in 130 Cases, J. Invest. Dermat. **4**:43-57, 1941.

3. Moore, M.: Personal communication to the authors.

In our series, M. audouini infections were far more frequent in the male, and the age group most frequently affected was that of 5 to 10 years. As would be expected, the scalp was the chief site of infection.

MICROSPORUM CANIS

The largest number of cases of infection with M. canis was reported from Oklahoma City. The sex incidence was approximately equal. In no case of infection in a patient over 15 years of age was the scalp involved. In the younger age group the scalp was the chief site of infection, but glabrous lesions were seen to occur with more frequency than with M. audouini, and there was a greater tendency for lesions to be inflammatory and to cause kerions. The tendency of this organism to produce inflammatory lesions is well known and has been previously recorded.[4] It is apparent that M. canis is the more frequent cause of tinea capitis in the western sectors of our survey.

MICROSPORUM GYPSEUM (FULVUM)

Infections with M. gypseum were too few to permit generalization, but all were observed in young children, and the scalp was involved in three of the five observed cases.

EPIDERMOPHYTON FLOCCOSUM

Again, too few cases of infection with E. floccosum were seen to permit any conclusions, except that the well-known tendency of this organism to cause pedal and crural infections was observed. The traditional form of crural involvement [5] was seen less frequently than that caused by T. rubrum.

Karrenberg [6] reported, in 1928, that most cases of epidermophytosis in Europe were due to E. floccosum. Mitchell [7] and Cleveland,[8] however, found an almost equal incidence of positive cultures for the T. mentagrophytes group and E. floccosum. In our series, E. floccosum was not observed with such frequency, and our incidence was in agreement with a more recent report [9] which gave the following percentages for positive cultures in material from the hands and feet: T. mentagrophytes, 75.4%, T. rubrum, 22.4%, E. floccosum, 1%, and C. albicans, 1%.

TRICHOPHYTON RUBRUM (PURPUREUM)

Infections with T. rubrum were found with discouraging frequency. Perhaps the high incidence is more apparent than real, for such infections are often difficult to cure and so may accumulate by virtue of treatment failure. This infection was predominant in males, and a notable feature was its chronicity. Thirty-eight per cent of our patients had carried the infection for more than two years. An additional 47% had been infected from six months to two years.

4. Lewis, and Hopper,[1] p. 74.

5. Lewis and Hopper,[1] p. 287.

6. Karrenberg, C.: The Present Status of Epidermophytosis in Europe: Results of Inquiry Concerning Numerical Occurrence of Epidermophytosis, Different Causative Fungi and Various Clinical Aspects, Arch. Dermat. & Syph. **17**:519-532, 1928.

7. Mitchell, J. H.: Further Studies on Ringworm of the Hands and Feet, Arch. Dermat. & Syph. **5**:174-197, 1922.

8. Cleveland, D. E. H.: Ringworm of the Hands and Feet, Canad. M. A. J. **17**:68-72, 1927.

9. Lewis and Hopper,[1] p. 91.

Not only did T. rubrum often infect the feet and crural regions but it also frequently infected the hands and nails.[10] Usually only one hand was involved and frequently one or more nails of the hand. Presumably, infection of the hands occurred by transfer, as patients with such infections usually showed preceding pedal or crural involvement. Although T. rubrum most frequently caused an erythematosquamous type of involvement, one of us (W. E. W.) obtained it on culture from vesicular lesions on four occasions.

In our series there were five patients in whom T. rubrum had occurred in a mixed infection. Although the other organisms in mixed infections varied, T. rubrum was always present.

Superficial Fungus Infections in Three Areas of Midwestern United States

Organism	St. Louis	Springfield	Oklahoma City	Total
M. audouini	107	3	5	115
M. canis	30	33	95	164
M. gypseum	1	1	3	5
E. floccosum	4	9	4	17
T. rubrum	17	70	50	137
T. mentagrophytes	17	35	53	105
T. sulfureum	1	1	2	4
T. crateriforme	0	0	1	1
T. faviforme	1	3	2	6
Achorion schoenleini	0	0	2	2
A. quinckeanum	2	0	0	2
Candida (species not identified)	9	30	70	109
Aspergillus (species not identified)	0	1	5	6
Geotrichum (species not identified)	0	1	0	1
	195	187	292	674

TRICHOPHYTON MENTAGROPHYTES (GYPSEUM)

Infections with T. mentagrophytes were of a briefer and more inflammatory nature. As expected, the feet were most frequently involved, but no area was spared. Infections of the nails and scalp were found.

CANDIDA (MONILIA)

Candida was obtained frequently on culture and was the only one which occurred more frequently in the female. This fact is in agreement with other studies.[11] In addition to the widespread sites of skin involvement the mucous membranes were often involved, particularly in the vaginal tract. Our figures certainly do not give a true picture of the frequency of vaginal involvement, for most of the patients with such infections are not treated by the dermatologist. Typical erosio interdigitalis blastomycetica was rarely seen. Involvement of the fingernails and paronychial tissues was extremely common.

10. Lewis, G. M.; Montgomery, R. M., and Hopper, M. E.: Cutaneous Manifestations of Trichophyton Purpureum (Bang), Arch. Dermat. & Syph. **37**:823-839, 1938.

11. Mitchell, J. H.: Erosio Interdigitalis Blastomycetica, Arch. Dermat. & Syph. **6**:675-679, 1922.

MISCELLANEOUS INFECTIONS

Infections with the rest of the organisms in the Table were infrequent, and the findings do not permit generalization. It is apparent that the epidemic of endothrix infections in the southwestern United States [12] has not yet reached the Midwest. Of interest is the fact that the two patients infected with Achorion quinckeanum were sisters and gave a history of similar involvement in other members of their family. The family resided near Sikeston, in southeast Missouri, an area described as being endemic for this organism.[13] The Aspergillus infections were noted in toenails and fingernails and, in two patients, in the external auditory canals.

COMMENT

It is of interest not only to compare this series with other published studies in the United States but also to compare it with data from other countries.

Weidman [14] attempted an extensive catalog of such information. He included that E. floccosum was not so important an organism as it had been thought to be by Sabouraud [15] and Whitfield [16] and noted that T. mentagrophytes was the most frequent cause of infection in the northern United States. In the southern United States, Manchuria, and Japan he found the commonest organism to be T. rubrum.

A more recent summary was published in England.[17] In this study, M. audouini was the most frequent cause of tinea capitis and E. floccosum of dermatophytosis (athlete's foot).

A report from Canada [18] showed infections with M. audouini and M. canis to be equally frequent. Surprisingly however, 40% of the cases of tinea capitis reported in this study were due to either Trichophytons or Achorions.

SUMMARY

A compilation and brief discussion of the cases of superficial fungus infections observed in three areas of the midwestern United States is presented.

Comparative reports for other areas in the United States and for other countries have been included and briefly analyzed in relation to this series.

12. Lehmann, C. F.; Pipkin, J. L.; Ressmann, A. C., and Kligman, A. M.: Tinea Capitis: The Endothrix Infections (Lantern Slide), presented before 45th Annual Meeting, Southern Medical Association, Dallas, Texas, Nov. 5-8, 1951.

13. Moore, M.: Personal communication to the authors.

14. Weidman, F. D.: Laboratory Aspects of Epidermophytosis, Arch. Dermat. & Syph. **15**:415-450, 1927.

15. Sabouraud, R.: Eczematoid Ringworm of the Extremities and Groin, Brit. J. Dermat. **23**:384-401, 1911.

16. Whitfield, A.: Eczematoid Ringworm of the Extremities and Groin, Brit. J. Dermat. **23**:375-384, 1911.

17. Duncan, J. T.: A Survey of Fungous Diseases in Great Britain: Results from First Eighteen Months, Brit. M. J. **2**:715-718, 1945.

18. Burgess, J. F.: Fungus Infections of the Skin: Cultural Study of Flora of Ringworm, Arch. Dermat. & Syph. **12**:853-857, 1925.

OCCURRENCE OF GYNECOMASTIA IN CONJUNCTION WITH DERMATOLOGIC DISORDERS

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GYNECOMASTIA is known to occur in conjunction with a variety of diseases, including testicular tumor, hepatic cirrhosis and hepatitis, bronchogenic carcinoma, lung abscess, carcinoma of the adrenal cortex, transverse myelitis, hyperthyroidism, and chronic ulcerative colitis.[1] In addition, gynecomastia is a common manifestation of puberty and starvation, and it can be produced by the administration of certain hormones, including estradiol, diethylstilbestrol (Stilbestrol), methyltestosterone, desoxycorticosterone acetate, adrenal cortex extract, and chorionic gonadotropin.[2]

From the Department of Dermatology, University of Virginia Department of Medicine (Dr. Wheeler, Dr. Cawley, and Dr. Gray), and the Department of Dermatology, University of Michigan Medical School (Dr. Curtis).

1. (*a*) Bauer, F. K., and Goodwin, W. E.: Acne and Gynecomastia Following I^{131} Therapy for Hyperthyroidism, Correspondence, J. Clin. Endocrinol. **11**:1574 (Dec.) 1951. (*b*) Cooper, I. S., and Hoen, T. I.: Gynecomastia in Paraplegic Males: Report of 7 Cases, ibid. **9**:457 (May) 1949. (*c*) Gilbert, J. B.: Studies in Malignant Testis Tumors: Syndrome of Choriogenic Gynecomastia; Report of 6 Cases and Review of 129, J. Urol. **44**:345 (Sept.) 1940. (*d*) Kark, R. M.; Morey, G. R., and Paynter, C. R.: Re-Feeding (Nutritional) Gynecomastia in Cirrhosis of the Liver: Clinical Observations, Am. J. M. Sc. **222**:154 (Aug.) 1951. (*e*) Karsner, H. T.: Gynecomastia, Am. J. Path. **22**:235 (March) 1946. (*f*) Klatskin, G., and Rappaport, E. M.: Gynecomastia Due to Infectious Hepatitis of the Homologous Serum Type, Am. J. M. Sc. **214**:121 (Aug.) 1947. (*g*) Kyle, L. H.: Gynecomastia in Association with Ulcerative Colitis, New England J. Med. **240**:537 (April) 1949. (*h*) Rose, E.; Dohan, F. C.; Zintel, H. F., and Eiman, J. W.: Estrogen-Producing Tumors of the Adrenal: Report of 4 Cases, abstracted, J. Clin. Endocrinol. **11**:798 (July) 1951.

2. (*a*) Jacobs, E. C.: Gynecomastia Following Severe Starvation, Ann. Int. Med. **28**:792 (April) 1948. (*b*) Jung, F. T., and Shafton, A. L.: Mastitis, Mazoplasia, Mastalgia, and Gynecomastia in Normal Adolescent Males, Illinois M. J. **73**:115 (Feb.) 1938. (*c*) Klatskin, G., and Munson, P. L.: Experimental Production of Gynecomastia with Chorionic Gonadotropin, Yale J. Biol. & Med. **24**:474 (June) 1952. (*d*) Maddock, W. O., and Nelson, W. O.: The Effects of Chorionic Gonadotropin in Adult Men: Increased Estrogen and 17-Ketosteroid Excretion, Gynecomastia, Leydig Cell Stimulation and Seminiferous Tubule Damage, J. Clin. Endocrinol. **12**:985 (Aug.) 1952. (*e*) McCullagh, E. P., and Rossmiller, H. R.: Methyl Testosterone: Androgenic Effects and the Production of Gynecomastia and Oligospermia, ibid. **1**:496 (June) 1941. (*f*) Raleigh, G. W., and Philipsborn, H. F., Jr.: Addison's Disease with Partial Absence of the Adrenal Cortex and Gynecomastia, Arch. Path. **37**:213 (March) 1944. (*g*) Van Heuverswyn, J.; Folley, S. J., and Gardner, W. U.: Mammary Growth in Male Mice Receiving Androgens, Estrogens and Desoxycorticosterone Acetate, Proc. Soc. Exper. Biol. & Med. **41**:389 (June) 1939.

The purpose of this paper is (*a*) to report seven patients in whom gynecomastia developed in conjunction with generalized dermatologic disorders, (*b*) to discuss briefly the etiology of gynecomastia, and (*c*) to consider the significance of gynecomastia when it occurs in association with generalized cutaneous diseases.

REPORT OF CASES

CASE 1.—*Generalized Atopic Dermatitis*

This patient, a white man, had atopic dermatitis during the summer months only when between the ages of 9 and 38 years. The dermatitis became generalized and persisted throughout the year between the ages of 38 and 40. Left gynecomastia developed at the age of 40, and the enlarged breast was surgically removed. The dermatitis was relatively quiescent between

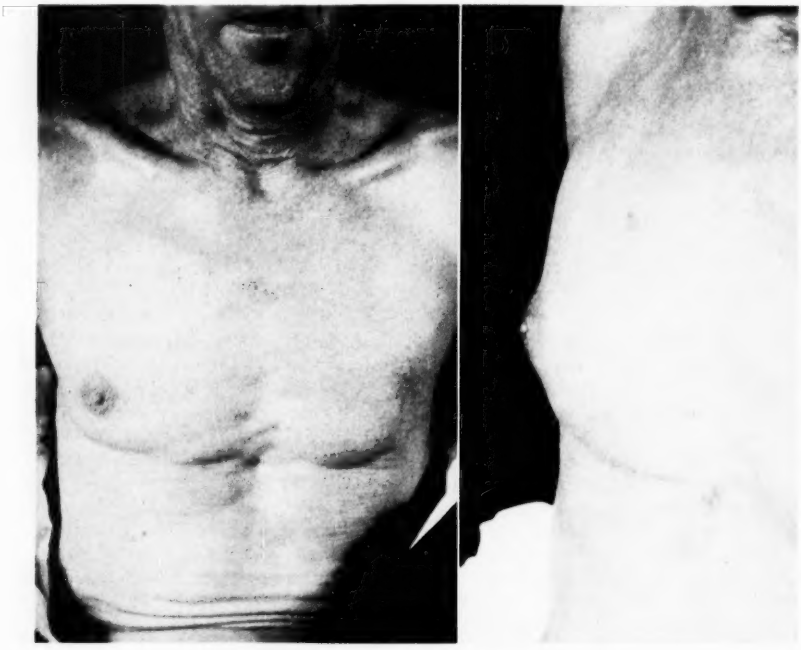

Fig. 1 (Case 1).—*A*, generalized atopic dermatitis, right gynecomastia, and scar at the site of removal of the left breast. *B*, profile showing enlargement of the right breast.

the ages of 40 and 43, but a severe exacerbation occurred at the age of 43. During the next six months the patient lost 23 lb. (10.4 kg.); the remaining right breast enlarged, and the scalp, beard, axillary, pubic, and body hair stopped growing. Physical examination six months after this exacerbation showed a generalized dermatitis; enlargement of cervical, axillary, epitrochlear, and inguinal lymph nodes; sparse scalp, beard, axillary, pubic, and body hair; mild edema of the face and legs; right gynecomastia, and a scar at the site of previous removal of the left breast. The chest was emphysematous, and there were expiratory wheezes throughout the lung fields. The testicles were normal; the spleen and liver were not palpable, and the blood pressure was 140/90. Laboratory examinations gave the following results: The urine, complete blood cell count, prothrombin time, blood urea, carbon dioxide combining power, bromsulfalein retention, and results of Kepler's water test were normal. The cephalin flocculation test was 3+ at 48 hours; thymol turbidity 3.1 units; blood cholesterol 189 mg. per 100 cc.; alkaline phosphatase 0.9 units; icterus index 6.0; total protein 5.7 gm. per 100 cc., and

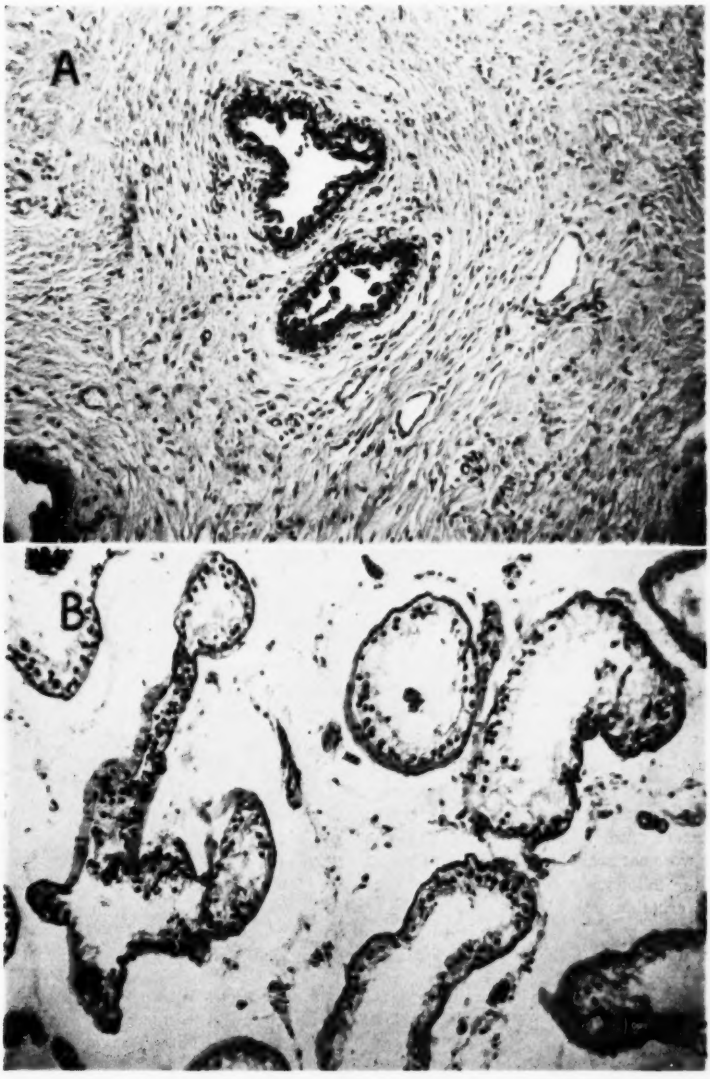

Fig. 2 (Case 1).—*A*, low-power photomicrograph of breast showing proliferation of the epithelium of the ducts, formation of new connective tissue, lymphocytic infiltration about the ducts, and increased vascularity. *B*, low-power photomicrograph of testicle showing atrophy of tubules and decreased spermatogenesis.

albumin-globulin ratio 1.7 : 1. Urinary gonadotropin was 3 units; urinary 17-ketosteroid excretion 6.0, 12.0, 7.0, and 9.8 mg. per 24 hours on four consecutive days, and urinary creatinine 0.69 and 1.1 mg. per 24 hours on two consecutive days. The chest x-ray showed emphysema, but the paranasal sinus x-rays were normal. Skin biopsies showed chronic nonspecific dermatitis, and lymph node biopsy showed dermatopathic lymphadenitis. Tissue from the right breast showed changes compatible with a diagnosis of gynecomastia, and a testicular biopsy revealed moderate oligospermia and some degree of tubular atrophy.

CASE 2.—*Contact Dermatitis with Autosensitization*

A 64-year-old white obese man had right gynecomastia three months after the onset of a generalized dermatitis (contact dermatitis with autosensitization). A clinical diagnosis of carcinoma of the male breast with metastases to axillary lymph nodes was made, and the right breast and right axillary nodes were removed. The pathologist reported changes in the breast tissue which were compatible with a diagnosis of gynecomastia; whereas the axillary lymph nodes showed alterations interpreted as those of dermatopathic lymphadenitis. The generalized dermatitis persisted, and the left breast enlarged four months after removal of the right breast. Physical examination seven months after onset of the dermatitis showed obesity, severe generalized dermatitis, operative scar at the site of removal of the right breast and axillary nodes, left gynecomastia, bilateral leg edema, generalized lymphadenopathy, and blood pressure of 148/90. The testicles were normal, and the liver and spleen were not palpable. The laboratory examinations showed a normal chest x-ray, normal urine, negative Kahn test, and normal blood cell count (except for 12% eosinophilia). The electrocardiogram was normal, except for left axis deviation. The skin biopsy showed chronic nonspecific dermatitis. The left breast was surgically removed, and the pathologist reported findings compatible with a diagnosis of gynecomastia.

CASE 3.—*Stasis Dermatitis with Autosensitization*

Right gynecomastia appeared in a 65-year-old white man two months after the onset of a generalized dermatitis (stasis dermatitis with autosensitization), and the left breast enlarged one month later. Physical examination three months after onset of the eruption showed generalized dermatitis, generalized lymphadenopathy, bilateral gynecomastia, bilateral leg edema, normal testicles, palpable liver edge, and blood pressure of 168/80. Laboratory examinations showed normal urine, normal blood cell count (except for mild leucocytosis), and a negative Kahn blood test. The chest x-ray was normal and x-rays of the spine revealed hypertrophic arthritis. Two skin biopsies showed nonspecific dermatitis, and a lymph node biopsy showed dermatopathic lymphadenitis. As the dermatitis improved, the right gynecomastia disappeared, and the left breast decreased in size.

CASE 4.—*Generalized Psoriasis*

An 80-year-old white man had right gynecomastia one month after the onset of generalized psoriasis. The patient had taken digitalis because of arteriosclerotic heart disease for an indefinite period before onset of the gynecomastia, but exact data concerning the history of his cardiac disorder were not available. Physical examination and laboratory studies, which were incomplete, showed the following results one month after onset of the generalized psoriasis: There was a universal eruption which showed the clinical characteristics of psoriasis; the testicles were normal; the liver and spleen were not palpable; the blood pressure was 120/70, and right gynecomastia was present. The results of urinalysis were normal, except for the presence of a large number of white blood cells; the chest x-ray was normal, and the electrocardiogram showed changes consistent with digitalis effect.

CASE 5.—*Angiodermatomyositis*

At the age of 39 this white man had a severe illness which was subsequently diagnosed as angiodermatomyositis. In the course of this illness the patient lost a great deal of weight and became bedfast. Physical examination at the height of the disease revealed widespread scleroderma-like skin changes, generalized lymphadenopathy, hepatomegaly, splenomegaly, muscle contractures, and atrophy, arthritis, xanthelasma, and bilateral epididymitis. The blood pressure was normal. Laboratory findings showed 1+ albuminuria, hemoglobin 9.8 gm. per 100 cc., red blood cells 3,300,000 per cubic millimeter, and an elevated sedimentation rate. The blood urea, nonprotein nitrogen, urea clearance, and bromsulfalein retention were normal. The total plasma cholesterol was 105 mg. per 100 cc.; globulin 4.7 gm. per 100 cc., and albumin-globulin ratio 0.93 : 1. X-rays showed right lower lobe pneumonitis; right pleuritis; osteoporosis of the bones

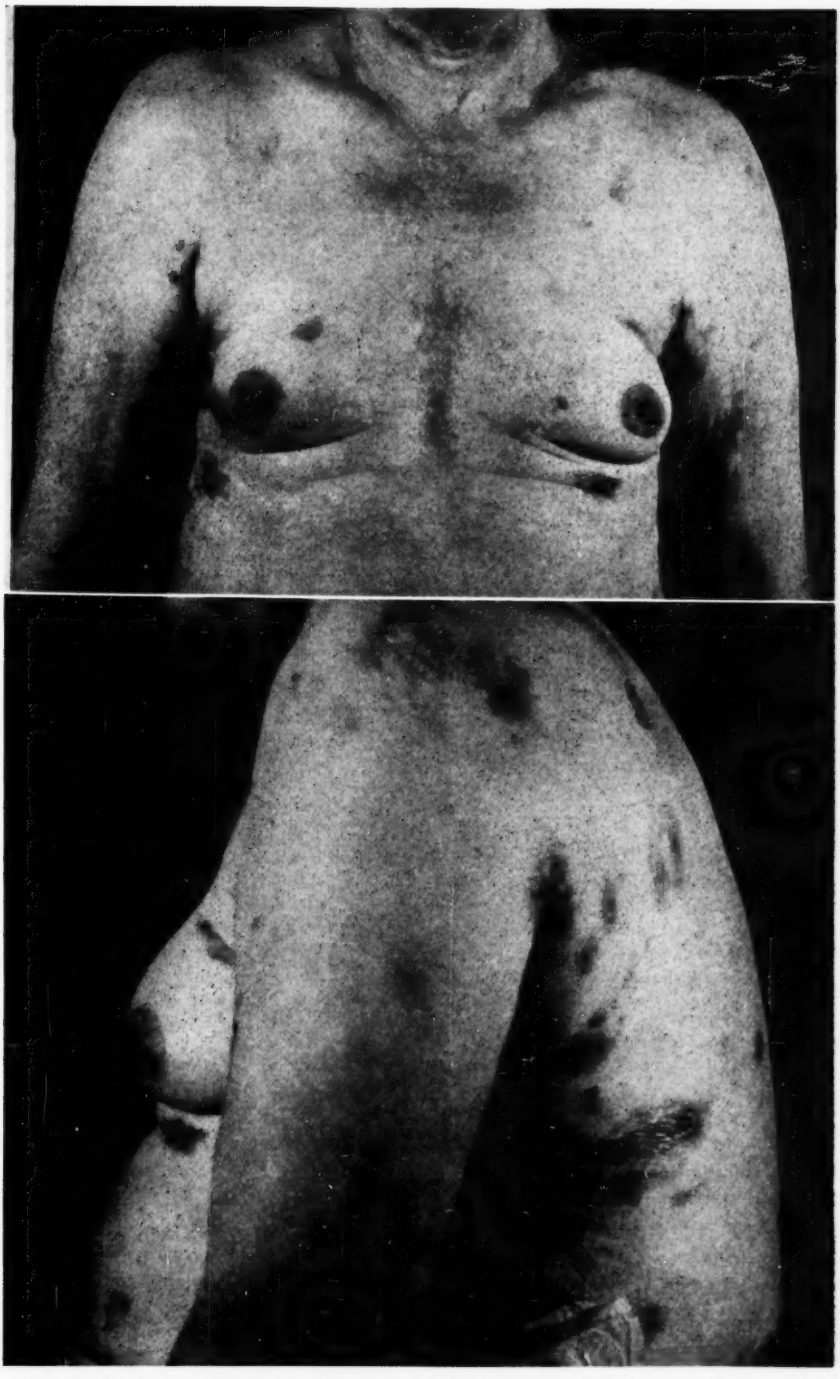

Fig. 3 (Case 7).—*A*, mycosis fungoides and bilateral gynecomastia. *B*, profile showing enlargement of the left breast.

of the hands, wrists, and feet, and calcification of the arteries of the lower legs. A biopsy of skin and muscle showed changes compatible with a diagnosis of angiodermatomyositis. Two years after onset of the disease, during a remission which apparently resulted from treatment with paraaminobenzoic acid, the patient was ambulatory; the arthritis subsided; the sclerodermatous skin changes regressed; the pneumonitis disappeared; he regained a considerable amount of weight, and bilateral gynecomastia appeared. Laboratory findings at this time showed a moderately severe hypochromic anemia, 2+ albuminuria, normal urea clearance, blood cholesterol 105 mg. per 100 cc., urinary 17-ketosteroid excretion 6.8 mg. per 24 hours, normal urinary follicle-stimulating hormone, and normal urinary estrogen excretion.

CASE 6.—*Unclassified Collagen Disease*

This 55-year-old white man had had an unclassified type of collagen disease for two years and had lost 20 lb. (9.1 kg.) in the preceding year, when right gynecomastia developed. Physical examination two years after onset of the collagen disease showed emaciation; scleroderma-like changes involving the skin of the shoulders, arms, and hands; right gynecomastia, and Dupuytren's and Peyronie's contractures. The distal portions of the fingers were clubbed, and nasal polyps were present. The liver and spleen were not palpable, and the testicles were normal. Laboratory examinations gave the following results: The blood count was normal, except for 12% eosinophilia. Other laboratory studies showed normal urine, elevated sedimentation rate, and pulmonary vital capacity which was 25% of the normal. The values for urea clearance, phenolsulfonphthalein excretion, blood urea, serum calcium, and serum phosphorus were normal, and agglutinations for typhoid, paratyphoid, and brucellosis gave normal results. X-ray showed bilateral pulmonary fibrosis, pulmonary emphysema, pleural thickening at the left base, bilateral maxillary sinusitis, normal teeth, and a normal gastrointestinal tract. Tissue from the right breast showed a microscopic picture compatible with a diagnosis of gynecomastia.

CASE 7.—*Mycosis Fungoides and Hypertension*

This 61-year-old white man, who had had mycosis fungoides for 13 years and hypertension for 4 years, had bilateral gynecomastia at an unspecified time in the course of his illness. Physical examination at the age of 61 showed widespread cutaneous lesions of mycosis fungoides and bilateral gynecomastia. Each testicle was approximately one-half to two-thirds normal size, and the blood pressure ranged between 150/90 and 200/110. The liver and spleen were not palpable. Laboratory examinations gave the following results: The blood cell count was normal, except for mild hypochromic microcytic anemia. Other laboratory studies showed normal urine, elevated sedimentation rate, blood urea 28 mg. per 100 cc., icterus index 4, total serum protein 7.0 gm. per 100 cc., albumin 3.8 gm. per 100 cc., globulin 3.2 gm. per 100 cc., cephalin flocculation ± at 48 hours, normal bromsulfalein excretion, negative Wassermann test, and normal chest x-ray. Urinary 17-ketosteroid excretion was 6.6 mg. per 24 hours. Several skin biopsies showed findings consistent with the diagnosis of mycosis fungoides. A bone marrow aspiration biopsy gave normal results, with the exception of an increase in eosinophiles. Testicular biopsy revealed azoospermia and mild atrophy of the seminiferous tubules.

ETIOLOGY OF GYNECOMASTIA

Available evidence indicates that gynecomastia may result from (*a*) the administration of various hormones, (*b*) physiologic mechanisms, and (*c*) pathologic processes which interfere with normal hormonal control. The administration of estrogens (estradiol, estrone, diethylstilbestrol), androgens (methyltestosterone, testosterone, testosterone proprionate), adrenal hormones (desoxycorticosterone acetate, adrenal cortex extract), and chorionic gonadotropin may cause gynecomastia.[3] Gynecomastia of physiologic type may occur in the newborn infant, probably as a result of transplacental passage of hormones from the mother to the fetus, and gynecomastia is a common manifestation of puberty, probably because of hormonal

3. Wheeler, C. E.; Cawley, E. P., and Curtis, A. C.: The Effects of Topically Applied Hormones on Growth, Pigmentation and Keratinization of the Nipple and Areola, J. Invest. Dermat. **20**:385 (May) 1953. Footnote *2c*, *d*, *e*, *f*, and *g*.

changes during this period.[4] The pathologic processes which may result in gynecomastia are numerous. Adrenocortical tumors (usually carcinomas) and adrenocortical hyperplasia give rise to gynecomastia because of excessive elaboration of adrenocortical hormones (estrogens of adrenal origin included).[1b] Testicular tumors, especially chorionepitheliomas, produce gynecomastia because of the secretion of large amounts of chorionic gonadotropin.[1e] Hepatic disease (cirrhosis, hepatitis) diminishes the ability of the liver to inactivate estrogen, thus permitting excessive amounts of estrogen to accumulate in the circulation and thereby cause gynecomastia.[5] Deficiencies of protein and vitamin B in the diet may interfere with hepatic function in a similar manner.[5a] Surgical removal or inflammatory destruction of testicular tissue and testicular atrophy (especially atrophy of the tubules) may produce gynecomastia. It has been suggested that the loss of Leydig cells results in a relative excess of estrogen which produces gynecomastia and that the loss of seminiferous tubules results in decreased production of a hormone called inhibin, which normally exerts an inhibitory effect on the gynecomastia-producing action of androgenic hormones.[6] Gynecomastia may also appear during starvation or during the period of refeeding that follows starvation.[7] The reason for the gynecomastia of starvation and refeeding is not known, but current explanations involve such theories as failure of the malnourished liver to detoxify estrogenic hormones, temporary overactivity of the adrenals or pituitary, and temporary underactivity of the testicles. Little is known about the mechanisms involved in the production of gynecomastia in such diseases as lung abscess, transverse myelitis, bronchogenic carcinoma, chronic ulcerative colitis, and hyperthyroidism, but again it is probable that abnormalities of hormonal control are involved.[8]

SIGNIFICANCE OF GYNECOMASTIA WHEN IT OCCURS IN ASSOCIATION WITH GENERALIZED CUTANEOUS DISEASES

The appearance of gynecomastia in a patient with a generalized dermatologic disorder probably indicates that normal hormonal control has been disturbed in some way by the dermatologic disease, since the known causes of gynecomastia involve hormonal changes of one type or another. Studies pertinent to the etiology

4. (*a*) Bruner, J. A.: Distribution of Chorionic Gonadotropin in Mother and Fetus at Various Stages of Pregnancy, J. Clin. Endocrinol. **11**:360 (April) 1951. (*b*) Rupp, J.; Cantarow, A.; Rakoff, A. E., and Paschkis, K. E.: Hormone Excretion in Liver Disease and in Gynecomastia, ibid. **11**:688 (July) 1951. (*c*) Jung and Shafton.[2b]

5. (*a*) Biskind, G. R., and Biskind, M. S.: The Nutritional Aspects of Certain Endocrine Disturbances, Am. J. Clin. Path. **16**:737 (Dec.) 1946. (*b*) Evans, J. M.; Young, J. P.; Hertz, R.; Tullner, W. W.; Wilmer, G., and Wood, O.: The Ability of the Human Liver to Reduce Biologic Activity of Injected Estrogens, J. Clin. Endocrinol. **12**:495 (May) 1952. (*c*) Glass, S. J.; Edmondson, H. A., and Soll, S. N.: Sex Hormone Changes Associated with Liver Disease, Endocrinology **27**:749 (Nov.) 1940. (*d*) Klatskin and Rappaport.[1f] (*e*) Rupp, Cantarow, Rakoff, and Paschkis.[4b]

6. Grabstald, H., and Swan, L. L.: Genitourinary Lesions in Leprosy, J. A. M. A. **149**:1287 (Aug. 2) 1952. Klinefelter, H. F., Jr.; Reifenstein, E. C., Jr., and Albright, F.: Syndrome Characterized by Gynecomastia, Aspermatogenesis Without A-Leydigism, and Increased Excretion of Follicle-Stimulating Hormone, J. Clin. Endocrinol. **2**:615 (Nov.) 1942. de la Balze, F. A.; Arillaga, F. C.; Irazu, J., and Mancini, R. E.: Klinefelter's Syndrome: A Study of 5 Cases, ibid. **12**:1426 (Nov.) 1952.

7. Jacobs.[2a] Kark, Morey, and Paynter.[1d]

8. Footnote 1*a*, *b*, *e*, and *g*.

of gynecomastia were performed infrequently in this series of patients, but those which were done point to altered function of the adrenals (low 17-ketosteroid values [Cases 1, 5, and 7]), testicles (tubular atrophy [Cases 1 and 7]), and liver (low serum cholesterol and reversal of the albumin-globulin ratio [Case 5]) as an explanation for the gynecomastia in the specified cases. In addition, analysis of the seven cases of this report suggests that some of the same poorly understood mechanisms which are involved in the production of gynecomastia during starvation and refeeding may be operative in the production of gynecomastia in generalized dermatitis; protein deficiency (and perhaps other deficiencies) may develop in patients with generalized dermatitis, because large amounts of protein are lost by exfoliation of the epidermis and exudation of serum, and debilitating illnesses, such as the collagen diseases and mycosis fungoides, may produce a state which is closely akin to starvation. On occasion (Case 5) the gynecomastia may appear when the debilitating disease is in remission and the patient is gaining weight, a circumstance similar to refeeding after starvation.

SUMMARY

The occurrence of gynecomastia in conjunction with generalized dermatologic disorders is reported.

The etiology of gynecomastia is briefly discussed.

The significance of gynecomastia when it occurs in association with generalized cutaneous diseases is considered.

PULMONARY HILAR ENLARGEMENT ASSOCIATED WITH WEBER-CHRISTIAN DISEASE

Report of a Case

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A REVIEW of the medical literature reveals that approximately 55 cases of nodular nonsuppurative panniculitis (Weber-Christian disease) have been reported to date. None of these reports presented any radiological findings of note. In the case to be discussed here, however, certain intrathoracic roentgenographic manifestations are exhibited which have not been described in any of the cases reported elsewhere. For this reason, it is felt that it is worth while to record a full description of this additional case of nodular nonsuppurative panniculitis.

Relapsing febrile nodular nonsuppurative panniculitis is characterized [1] by recurrent episodes of fever, the temperature ranging as high as 104 F., associated with the appearance of single to multiple crops of subcutaneous nodules, varying from the size of a pea to several inches in diameter, usually occurring on the thighs and arms and frequently on the abdomen, back, and legs. The nodules, tender or painless, are freely movable and are located in the panniculus adiposus. They are frequently erythematous and raised above the surface of the normal skin. The nodules do not produce pus and may regress in a few days or weeks, either leaving a shallow dimple in the skin or showing no superficial evidence of their site.

Relapses occur at intervals as short as a few weeks and as long as several years. There are no prodromal symptoms.

As a rule, no pathological changes are observed in other systems of the body, although death from the disease per se has been reported in several instances. The findings at postmortem examination in several of these cases to be discussed below are important as a possible explanation of the roentgenographic changes seen in the case to be reported here.

The etiology of the disease is in doubt. In a review of 44 cases, Bendel [1a] found that the disease had occurred in 34 females and 10 males. Of the total, nine patients

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Sponsored by the Veterans Administration with approval of the Chief Medical Director. Statements and conclusions by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. (*a*) Bendel, W. L., Jr.: Relapsing Febrile Nodular Panniculitis (Weber-Christian Disease): Review of the Literature and Report of a Case, Arch. Dermat. & Syph. **60**:570-596 (Oct.) 1949. (*b*) Hallahan, J. D., and Klein, T.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Review of Literature and Report of Case, Ann. Int. Med. **34**:1179-1201 (May) 1951.

were below the age of 20 and only three were infants. The greatest number of patients were in the fourth and sixth decades of life. The various etiological factors incriminated [2] included halogen sensitivity, local or systemic foci of infection, and bacterial, viral, or chemical allergy of some sort. No consistent endocrine disturbance, or blood chemical changes, or hematological changes have ever been demonstrated.

Almost every conceivable therapeutic procedure [1b] has been tried, but the efficacy of the treatment is difficult to be ascertained because of the characteristic periods of spontaneous remissions of the disease. Supportive and symptomatic treatment thus far is the form of therapy of value to the patient.

REPORT OF CASE

W. H., a 39-year-old married white man, a carpenter, was admitted to the Veterans Administration Hospital, Des Moines, Iowa, on Feb. 29, 1952, complaining of swollen painful feet and ankles. He had never been ill before, except for a history of malaria in World War II while serving in the Pacific theater of war. About two to three months prior to admission, he noted two or three separate episodes of chills and fever which felt much like the episodes of malaria, but which were less severe and which lasted only a few minutes to an hour, requiring no medication and followed by a normal feeling of well-being and ability to work at ordinary activities. On Jan. 31, 1952, he noted a severer chill, with fever lasting about an hour, requiring no medication. He worked the following day but felt tired in the afternoon. He continued to work for the next two weeks but did not feel well, and at that time he noted painful feet and ankles, which finally caused him to give up work. He was seen by his local physician and was given penicillin. Since he did not improve, the patient then sought and obtained admission here.

The pertinent physical findings were limited to the lower extremities. The ankles and feet disclosed an indurated swelling of the skin and subcutaneous tissue, with definite pitting edema about the tendo achillis. A red-purple indurated area, about 6 cm. in diameter, was present over the anterolateral aspect of the left ankle. About 5 cm. above the right ankle was a tender subcutaneous nodule which was firm and fixed and which was lying over the flat tibial surface of the leg. There was slight reddening of the overlying skin.

The results of the laboratory studies included a negative serological reaction for syphilis and a negative malarial smear. Blood urea nitrogen and uric acid levels were within normal limits. Urine was normal, and the Fishberg concentration test showed a maximum specific gravity of 1.022, with no albumin present. Complete blood cell counts gave normal results on three occasions. The sedimentation rate (Cutler method) was somewhat elevated upon admission, being 19 mm. in one hour, but in the second and ninth months after admission it had decreased to well within the normal range. Brucellosis agglutination was negative. Blood cultures failed to yield any growth on four different occasions. Sputum specimens did not show evidence of acid-fast bacilli on smear or culture. The first and second strength tuberculin tests gave negative results. Liver-function studies included total protein, albumin, globulin sulfobromophthalein (Bromsulphalein), cephalin flocculation, and thymol turbidity, and all gave normal results. Serum amylase and lipase levels were within normal limits.

X-ray examination of the chest on March 4, four days after admission, showed bilateral hilar enlargement, that on the right having a well-circumscribed lobulated or nodular appearance (Fig. 1). The etiology for this finding was not known, and the differential diagnosis included all the inflammatory and neoplastic diseases which were known to produce such changes. However, the complete clinical and laboratory work-up as well as the subsequent course of the patient's illness served to rule out these various possibilities.

On March 13 it was noted that there were several subcutaneous nodules in the left and right calves. One of the nodules in the left calf was selected for excisional biopsy. Microscopic

2. (*a*) Bendel.[1a] Hallahan and Klein.[1b] (*b*) Charache, H.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Syndrome), New York J. Med. **52**:1133-1136 (May 1) 1952.

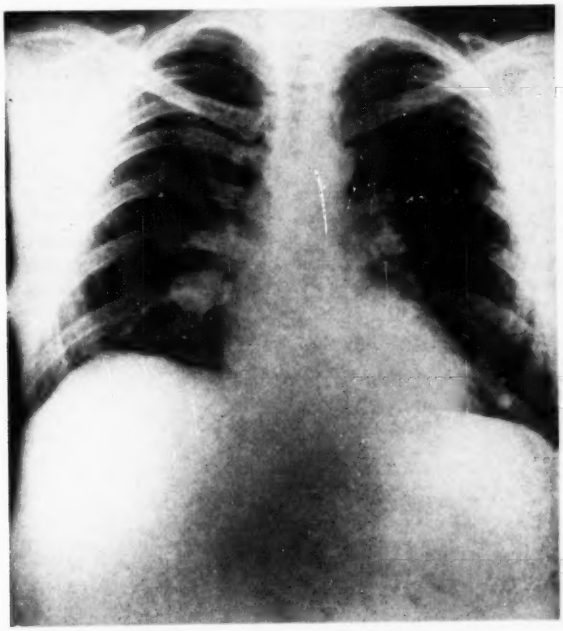

Fig. 1.—Roentgenograph of chest, March 4, 1952, showing bilateral hilar enlargement.

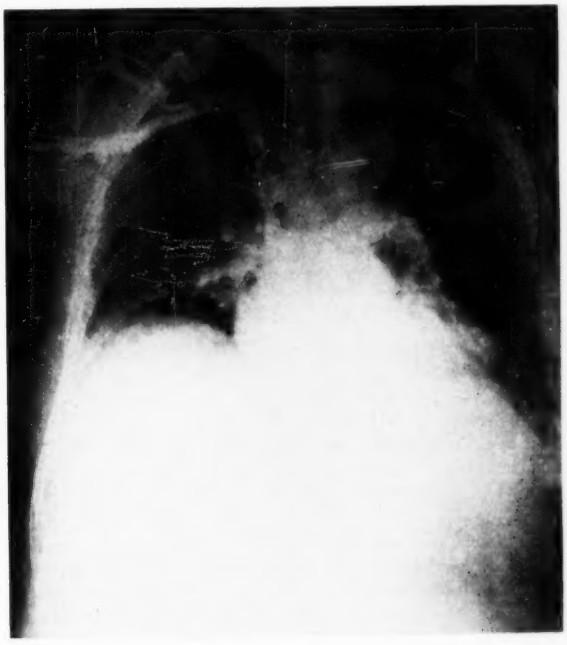

Fig. 2.—Angiocardiogram, April 10, 1952, showing normal vascular pattern at each lung root.

sections of this nodule revealed "strands of loose connective tissue in the subcutaneous adipose tissue. There is an occasional giant cell in this fat. Subintimal thickening of the smaller arteries is noted, and one shows some endothelial hyperplasia. Fat necrosis is present, often distant from the vessels." It was felt that the microscopic findings were compatible with nodular nonsuppurative panniculitis, and that the vascular reaction was secondary to the inflammatory changes and not the cause itself.

On the 18th hospital day, it was noted that the nodular areas in the legs had diminished in size and two new ones had appeared on the posterior aspect of the thighs, as well as two subcutaneous nodules above the left wrist, ulnar side.

On March 20, a second biopsy was performed. A subcutaneous nodule in the right calf was removed, and this, too, showed findings compatible with nodular nonsuppurative panniculitis. The material obtained at this time was smeared and cultured, and no organism was isolated.

Fig. 3.—Roentgenograph of chest, Dec. 11, 1952, showing complete remission, the hilar shadows being normal.

On the 24th hospital day, the nodules in the thighs had disappeared, and those in the calves had become less prominent. There was no more discoloration of the skin.

On April 10, an angiocardiographic examination was done (Fig. 2). This showed that the bilateral hilar prominences were extravascular, with no impingement upon the vessels in either lung root.

The patient was discharged and followed as an outpatient. During his hospital stay, the patient's temperature did not go above 99.4 F. After the second biopsy, the patient was empirically given a course of chloramphenicol (Chloromycetin) therapy, 500 mg. every six hours, but at this time the subcutaneous lesions had already largely begun to disappear. Except for his painful feet, which were due to pes planus, the patient was essentially asymptomatic throughout his hospital stay. X-ray examinations of his feet, ankles, wrists, and hands revealed no abnormalities.

In May, it was noted that the previously described nodules had gone. In addition, while the patient was at home one small nodule developed on his leg, which disappeared too.

On Dec. 11, approximately nine months after the initial chest examination, a roentgenograph of the chest showed a picture which was entirely within normal limits (Fig. 3). The hilar shadows, in marked contrast to the previous examination, had returned to normal proportions.

A review of the patient's service records and previous records of admission to this hospital reveals that febrile episodes have been a recurrent problem in this patient for many years. Indeed, there was no evidence on record of preexistent malarial infestation. In view of the course of the patient's illness and the pathological diagnosis of nodular nonsuppurative panniculitis, it may be logical to assume that the prior episodes of illness as well as the present illness constitute the clinical entity of chronic febrile relapsing nodular nonsuppurative panniculitis.

COMMENT

Reviews of the medical literature by Bendel,[1a] Hallahan and Klein,[1b] and Shuman,[3] as well as individual case reports [4] show that up to this report no case of nodular nonsuppurative panniculitis presented any evidence of pulmonary hilar enlargement as a feature of the disease. Indeed, there is no direct pathological proof that the x-ray findings reported here are a part of the disease process. However, when the autopsy findings of some of the patients who died of nodular nonsuppurative panniculitis are reviewed, a reasonable explanation for the hilar enlargement and remission can be forwarded.

Kritzler [5] was the first to do an autopsy on a patient with nodular nonsuppurative panniculitis. The patient was a 34-year-old woman. At autopsy, the liver appeared fatty and the spleen enlarged. There were fat emboli in the lungs, the cells of the adrenal cortex showed hydropic degeneration, and large numbers of erythrocytes were engulfed by cells of the reticuloendothelial system.

The case of fatal relapsing febrile nonsuppurative panniculitis reported by Mostofi and Engleman [6] disclosed widespread involvement of adipose tissue showing changes characteristic of this disease. The conspicuous lesions were found in the subcutaneous, epicardial, peripancreatic, periadrenal, perirenal, and mesenteric fat.

Spain and Foley [7] performed an autopsy on a patient who showed typical nodules not only in the subcutaneous layer, but in the mesenteric, pretracheal, and omental fat as well.

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3. Shuman, C. R.: Relapsing Panniculitis (Weber-Christian Disease): Review of Literature and Report of a Case Including Treatment with Cortisone, A. M. A. Arch. Int. Med. **87**:669-681 (May) 1951.

4. Birrell, J. H. W.: Weber-Christian Syndrome: Report of a Case, Medical Journal of Australia **2**:124-127 (July 26) 1952. Charache,[2b] Doerner, A. A., and others: The Development of Tuberculous Meningitis Following Cortisone Therapy, Am. Rev. Tuberc. **64**:564-571 (Nov.) 1951. Kennedy, R. J., and Murphy, L. R.: Weber-Christian Disease, Am. J. Med. **6**:672-689 (May) 1949. Kinmont, P. D. C.: Non-Suppurative Panniculitis, Brit. J. Dermat. **64**:108-109 (March) 1952. Rubin, S. H., and Bland, J. H.: Relapsing Febrile Nonsuppurative Panniculitis (Weber-Christian Disease), Am. J. Med. **7**:288-292 (Aug.) 1949.

5. Kritzler, R.: A Case of Weber-Christian Disease, Proceedings of the New York Pathological Society (abstract) 1941, p. 47.

6. Mostofi, F. K., and Engleman, E.: Fatal Relapsing Febrile Nonsuppurative Panniculitis, Arch. Path. **43**:417-426 (April) 1947.

7. Spain, D. M., and Foley, J. M.: Nonsuppurative Nodular Panniculitis (Weber-Christian's Disease), Am. J. Path. **20**:783-787 (July) 1944.

Thus, it is seen that the disease may involve not only the subcutaneous fat, but the visceral fat as well. It is felt, therefore, that the patient described in this paper had involvement of his intrathoracic fat tissue, probably in each lung hilus, producing the lobular enlargement seen on the chest roentgenograph. Remission of these enlargements is part of the natural history of the disease process, producing eventually a chest film which shows a normal picture.

SUMMARY

A case of nodular nonsuppurative panniculitis is presented with typical clinical and pathological findings.

The case is the first to be reported in which bilateral pulmonary hilar enlargement with subsequent remission is exhibited.

An explanation for the roentgenographic findings is offered.

EFFECT OF SPLENECTOMY IN ACUTE SYSTEMIC LUPUS ERYTHEMATOSUS

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HONOLULU, T. H.

THE SPLEEN has been a source for conjecture and confusion from both physiologic and pathologic standpoints. The participation of the spleen in various symptom complexes is still being debated and elucidated. About 20 years ago, Wise [1] and Keil [2] showed interest in the association of splenic malfunction, splenectomy, and lupus erythematosus. Within the last five years, isolated reports have appeared regarding the role of the spleen in the mysterious and often fatal syndrome, lupus erythematosus.

Several theories have been proposed regarding the relation of the spleen and bone marrow hemopoiesis. Dameshek and Estren [3] postulated that the spleen normally exerts on the bone marrow an inhibitory effect which may become increased in splenomegaly. Increase of this normal function is called hypersplenism. Dameshek and Estren [3] cited Morawitz and Eppinger, who suggested the word "hypersplenism" for the activity of the spleen associated with cytopenias. This activity inhibits hemopoiesis by "blocking" the escape of mature cells from the bone marrow. There may be a total reduction of all cell elements of the blood or a selective cytopenia, such as neutropenia, anemia, or thrombocytopenia. Dameshek and Estren [4] believed that the abnormal spleen secretes to excess a hormone which produces several types and degrees of cytopenias: (1) inhibition of maturation of megakaryocytes (splenic thrombocytopenia), (2) inhibition of delivery of granulocytes (splenic neutropenia), (3) inhibition of delivery and production of erythrocytes, and (4) destruction of old red cells.

Doan and Wright [5] suggested that the reticuloendothelial cells of the spleen may phagocytose the red and white blood cells, thrombocytes (platelets), ubiquitous bacteria, and toxic products. An increase of this physiologic phagocytosis and sequestration of cells may produce a pathologic diminution in one or more of the circulating elements in the blood.

Read before the meeting of the American Dermatological Association, Lake Placid, N. Y., June 9 to 13, 1953.

1. Wise, F.: Lupus Erythematosus Bullosus or Pemphigoides: Report of 2 Cases with Discussion of "Senear-Usher Syndrome," M. J. & Rec. **134**:227-231 (Sept. 2) 1931.

2. Keil, H.: Relation Between "Systemic" Lupus Erythematosus and a Peculiar Form of Thrombocytopenic Purpura, Brit. J. Dermat. **49**:221-237 (May) 1937.

3. Dameshek, W., and Estren, S.: The Spleen and Hypersplenism, New York, Grune & Stratton, Inc., 1947.

4. Dameshek, W., and Estren, S.: Symposium on Specific Methods of Treatment: Hypersplenism, M. Clin. North America **34**:1271-1289 (Sept.) 1950.

5. Doan, C. A., and Wright, C. S.: Primary Congenital and Secondary Acquired Splenic Panhematopenia, Blood **1**:10-26 (Jan.) 1946.

Johansen [6] demonstrated that the spleen, instead of secreting a hormone which inhibits the bone marrow, resorbs a factor that normally promotes the function of the bone marrow. In patients with hypersplenism, the circulating serum contains decreased amounts of this substance, which soon returns to normal quantities after splenectomy. The spleens of these patients contain an excessive amount of this factor; when pressed juice of such spleens was used as a nutrient medium in bone marrow culture, there was a 15% increase in the activity of the marrow as compared with normal marrow cultures in which serum was used as a nutrient medium.

Trice [7] suggested the actual production of a substance in the spleen or in the entire reticuloendothelial system which acts in a destructive manner in the peripheral bloodstream. He would classify this reaction as "hyperreticuloendotheliosis" instead of hypersplenism.

The incongruities of these theories and others suggest further investigation along similar lines. Research investigations and findings have been largely hypothetical and speculative to the present.

VALUE OF SPLENECTOMY IN HYPERSPLENISM

Splenectomy is not a simple procedure; still it cannot be construed as a dangerous one. Mortality rates as low as 4.3% have been listed,[8] and postoperative complications are unusual. This percentage is satisfactory, considering the serious diseases and the poor preoperative clinical condition of the patients, who often show such complications as thrombocytopenia and pancytopenia.

Surgery is frequently advocated in certain blood dyscrasias due to splenic disease. There may be alarming deficiencies of blood cells or thrombocytes that cannot be replenished by any other means. A successful result is the rule in many diseases if the diagnosis is confirmed by a competent hematologist, if there is excellent preoperative care, and if the surgeon is skilled.

It was thought at one time that only two medical conditions necessitate splenectomy, namely, idiopathic thrombocytopenic purpura and congenital hemolytic anemia. Recently,[9] the medical indications have been increased to include acquired hemolytic anemia, primary splenic hemocytopenia, selected cases of secondary panhemocytopenia, idiopathic neutropenia, and an occasional case of undetermined splenomegaly.

Splenectomy may produce dramatic clinical improvement and restoration of the hematologic picture to normal or near normal in a variety of conditions which demonstrate a decrease of one or more of the formed elements. These conditions have been termed varieties of hypersplenism or abnormal increase in splenic function.[10]

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6. Johansen, C.: A New Theory of Splenic Marrow Inhibition, in Proceedings of the International Society of Hematology, Third International Congress, Cambridge, England, 1950, New York, Grune & Stratton, Inc., 1951, pp. 108-111.

7. Trice, W. W.: Hypersplenism—Agranulocytosis and Miscellaneous Manifestations, J. Florida M. A. **39**:334-336 (Nov.) 1952.

8. Miller, E. M., and Hagedorn, A. B.: Results of Splenectomy: A Follow-up Study of 140 Consecutive Cases, Ann. Surg. **134**:815-821 (Nov.) 1951.

9. Lahey, F. H., and Norcross, J. W.: Splenectomy: When Is It Indicated? Ann. Surg. **128**:363-378 (Sept.) 1948.

10. Johnson, V. M.: Pathology of Hypersplenism, J. Florida M. A. **39**:341-343 (Nov.) 1952.

During the past seven years, I have been able to follow the results of 12 splenectomies performed as life-saving palliative measures for acute systemic lupus erythematosus. The dramatic results that followed the first two cases of idiopathic thrombocytopenic purpura,[11] plus the favorable clinical and hematologic change in other cases, form the basis of this report.

REPORT OF CASES

CASE 1.—L. M., a white married woman aged 37 years, was seen in March, 1946, with a history of chronic discoid lupus erythematosus for 12 years. She had recently become purpuric, with erythematous facial lesions. Malaise, weakness, and arthralgia were experienced and became progressively worse.

In Oct., 1946, the patient was hospitalized because of increased purpura with retinal hemorrhages which rapidly progressed to cause almost total blindness. The skin lesions were typical of acute systemic lupus erythematosus. The blood studies on admission showed 6 gm. of hemoglobin per 100 cc.; red cells numbered 1,800,000, and thrombocytes were decreased to 3,000, per cubic millimeter. The white blood cell count was 3,000 to 4,000, with 50% neutrophiles. Repeated transfusions had no effect on the neutropenia or thrombocytopenia. Her temperature increased to 103 F. Bleeding occurred from the nose, mouth, bladder, and vagina.

TABLE 1.—*Results of Splenectomy in Acute Systemic Lupus Erythematosus*

Case No.	Age, Yr.	Preoperative Condition	Postoperative Condition	Relief of Symptoms	Period of Benefit After Splenectomy	Duration of Life After Splenectomy
1.....	37	Moribund day of surgery	Good	Excellent	7 yr.	7 yr. (living)
2.....	22	Generalized purpura, acutely ill	Good	Good	2 mo.	2½ mo.
3.....	24	Acutely ill, comatose	Good	Good	50% for 2 yr.	2½ yr.
4.....	22	Critical	Fair	Good	3 mo.	3 mo.
5.....	18	Fair	Good	Good	7 mo.	8 mo.
6.....	17	Critically ill	Good	Excellent	4 mo.	12 mo.
7.....	23	Critical	Critical	None	0	5 days
8.....	38	Critical	Critical	None	0	9 days
9.....	16	Fair	Good	Good	2 mo.	3 mo.
10.....	16	Critically ill	Acutely ill	None	0	7 days
11.....	31	Critical	Poor	Fair	Partial (50%)	3 yr. (living)
12.....	30	Fair	Fair	Fair	Mild benefit, 2 yr.	2 yr. (living)

The spleen, weighing 140 gm., was removed by Dr. Douglas Bell on Nov. 13, 1946.

The immediate postoperative course was stormy, but the patient became cheerful and had little discomfort by the fourth postoperative day. Forty-eight hours after the splenectomy, the thrombocyte count rose to 51,000 per cubic millimeter. The white blood cells numbered 23,000, with 90% polymorphonuclear leucocytes. The purpura completely ceased, and the edematous blush of the face subsided. She rapidly gained weight and strength. Her vision and hemiplegia improved. The hemogram returned to normal.

Since the splenectomy (1946), the patient has maintained good health and has gained 40 lb. (18.1 kg.). She has had fleeting attacks of arthralgia and occasional erythema of the face. The blood counts have remained within normal limits during the last seven years.

CASE 2.—B. Y., a Japanese woman aged 22 years, was admitted to The Queens Hospital on March 15, 1947, because of a severe flare-up of lupus erythematosus. She had been hospitalized

11. Johnson, H. M.; Fujiwara, T. F., and Millard, R. D.: Hypersplenism and the Effect of Splenectomy in Acute Disseminated Lupus Erythematosus: Preliminary Report, Hawaii M. J. **9**:156-159 (Jan.-Feb.) 1950.

TABLE 2.—*Results of Hematologic Studies Before and After Splenectomy*

Case No.	Date	Thrombocytes, per Cu. Mm.		White Blood Cells, per Cu. Mm.		Red Blood Cells, Millions per Cu. Mm.		Hemoglobin, Gm. per 100 Cc.		Follow-Up Studies				
		Before	After	Before	After	Before	After	Before	After	Date	Thrombocytes, per Cu. Mm.	White Blood Cells, per Cu. Mm.	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, Gm. per 100 Cc.
1	11/10/46	36,000 3,000	59,000	4,000 3,000	23,100	2.9	3.9	8.4	10.5	1951 1952	393,000 229,000	12,450 10,850	4.1 3.9	11 13
2	3/28/47	16,000	140,000 262,000	5,000 4,000	10,000	3.24	4.2	9.2	....	May, 1947	543,000	6,300	5.2	13
3	7/29/47	186,000	445,000	4,300	12,000	2.8	4.2	6.5	....	1950	378,000	8,300	3.5	10.5
4	8/16/47	275,000	564,000	4,500	24,400	3.18	4.4	10.2	12	11/1/47	.....	14,500	4.2	11.2
5	8/18/47	185,000	.....	4,800	13,100	2.6	4.10	11	11	April, 1948	.....	10,200	1.7	4.5
6	11/23/47	355,000	539,000	3,900	12,100	3.5	4.13	8.5	....	12/25/48*	Many normal blood cell counts			
7	1/5/48	171,000	.....	3,200	31,400*	3.10	4.68	11	12.6	....	Died on 5th postoperative day			
8	5/16/48	128,750	594,000	4,250 3,850	5,500	3.03	2.8	6.1	8.8	....	Died on 9th postoperative day			
9	5/12/50	.....	.....	3,900 2,650	8,205 11,050	3.13	4.2	7.5	....	8/17/50*	Many normal blood counts			
10	9/18/50	75,240 37,620	236,300	3,600 1,900	10,900	3.10	4.6	8.5	....	....	Died on 7th postoperative day			
11	4/18/50	180,000	.....	5,500 2,000	12,500 9,400	3.3	3.2	5.5	9.6	1951 1952 1953	.... Normal hemograms	7,100 6,350	4.8 3.7	.. ..
12	4/29/51	365,820	358,000	6,700 5,000	7,150	3.5	3.9	9	10	1951-1952 1953	Normal hemograms Normal hemograms			

* Date of death.

previously because of a similar but milder attack. The patient's temperature spiked to 104 F., and her condition became critical. She began manifesting extensive purpura. The red blood cell count dropped to 3,400,000, and the thrombocyte count was 16,000, per cubic millimeter. The bleeding time was 16 minutes. Clotting time was normal; there was no clot retraction after 24 hours.

Splenectomy was performed on March 31, 1947. The patient's condition was extremely critical, and not much hope was held for her recovery. No evidence of purpura was encountered after the splenectomy, and the thrombocyte count rose from 140,000 per cubic millimeter 24 hours after the operation to 262,000. All elements of the bone marrow became normal in seven days.

In two weeks the temperature returned to normal, and the patient was improved both subjectively and clinically. The skin lesions completely regressed. She was discharged from the hospital 35 days after the operation, free from all symptoms except a dull epigastric pain.

Three weeks later she was hospitalized again, with severe epigastric pain as the only complaint. Her hemogram was within normal limits. The thrombocyte count was 543,000 per cubic millimeter. The sedimentation rate was 22 mm. in one hour. Serum albumin measured 2.9 gm., and serum globulin, 2.8 gm., per 100 cc. Urinalysis revealed the presence of albumin (3+), leucocytes, and red blood cells.

Fig. 1 (Case 1).—Patient is relatively asymptomatic seven years after splenectomy.

She suddenly died in severe shock on the 16th hospital day. Postmortem examination revealed that death was caused by a massive hemorrhage into the peritoneal cavity from the splenic pedicle. The injury was produced during the splenectomy, when the tail of the pancreas was inadvertently nicked, allowing a slow escape of pancreatic fluid.

Case 3.—C. C., a 24-year-old Japanese housewife, was admitted to Kuakini Hospital because of a spontaneous abortion, with the additional complaints of arthralgia, elevation in temperature to 101 to 104 F., rash on the face and back, and palpable nodes in the neck. The heart was grossly enlarged, and a pericardial friction rub was heard. The red blood cell count was 2,870,000. The hemoglobin concentration was 6.5 gm. per 100 cc. White blood cells ranged from 4,300 to 5,650 per cubic millimeter, with 78% polymorphonuclear leucocytes and 22% lymphocytes. The thrombocyte count was 186,000 per cubic millimeter. Urinalysis revealed a trace of albumin and many red blood cells. The Kline serologic test had a negative result. Cholesterol measured 197 mg. per 100 cc. of blood. A culture of the blood revea'ed no pathogens.

The spleen was removed on Aug. 1, 1947. Within two days, there was a drop in temperature and the pulse rate and all joint pains were decreased. The skin lesions were subsiding and paler. The hemogram returned to normal limits. The thrombocyte count was 445,000 per cubic millimeter.

The patient was afebrile in three weeks and was discharged from the hospital in good condition. She had many episodes of severe chest pain, necessitating heavy dosage of meperidine (Demerol) hydrochloride for its relief, until she became addicted to the drug. The patient was readmitted to the hospital by Dr. H. M. Izumi on March 8, 1948, complaining of edema of the

Fig. 2 (Case 2).—Before splenectomy. Patient was acutely ill and had generalized purpura and facial edema.

Fig. 3 (Case 2).—One month after splenectomy. Patient showed excellent clinical response.

face, arms, legs, and abdomen and severe chest pains. The hemogram was within normal limits. The sedimentation rate was 26 mm. in one hour; urinalysis showed albumin (4+) and a few white blood cells, red blood cells, and granular casts. The total protein was 8.8 gm. per 100 cc. (4.78 gm. of albumin and 4.09 gm. of globulin).

The patient lived until March 12, 1950, and died of cardiac decompensation and glomerulonephritis.

CASE 4.—J. B., a Filipino housewife aged 22, first noted in 1946 an indolent erythematous lesion of the face after a day at the beach. Within the last year several additional lesions had appeared, associated with fever, arthralgia, and weakness. Sunlight definitely produced a burning sensation, even on short exposures.

On her admission to the hospital, Aug. 8, 1947, the patient was profoundly ill, the temperature ranging between 102 and 106 F. and a weak thready pulse of 140 per minute. The face was erythematous and edematous. Chest examination revealed evidence of bronchopneumonia and polyserositis. The hemogram showed 3,180,000 red blood cells per cubic millimeter. The hemoglobin concentration was 10.2 gm. per 100 cc. The white blood cell count ranged from 4,500 to 6,800, with a normal differential count. Thrombocytes numbered 275,000 per cubic millimeter. Urinalysis showed nothing abnormal. A clinical diagnosis of acute systemic lupus erythematosus was suggested by Dr. H. Arnold Jr.

The spleen was removed on Aug. 19, 1947, as a last measure, and the patient was classed as a poor surgical risk.

She was seriously ill for five to seven days postoperatively because of a complicating pneumonia. On the 12th postoperative day the temperature returned to normal with only an occasional rise to 101 F. On Sept. 4, 1947, or 16 days postoperatively, Dr. Arnold said, "The rash, joint pains, and leukopenia have vanished. Her course is consistent with remission induced by splenectomy." The patient had a temporary setback when a toxic psychosis with hallucination developed. This complication was thought to be the result of secondary cerebroarteriolar damage due to the systemic disease. She left the hospital on Oct. 11, 1947, or three weeks after splenectomy; her temperature was normal, and she felt fairly well.

The laboratory examination after operation showed 4,110,000 red blood cells and 24,400 white blood cells per cubic millimeter, with 92% polymorphonuclear leucocytes and 8% lymphocytes. The hemoglobin concentration was 12 gm. per 100 cc. The thrombocyte count was 564,000 per cubic millimeter. Cholesterol measured 80 mg. per 100 cc. of blood. No abnormality was demonstrated on urinalysis.

On Nov. 1, 1947, she was again admitted to the hospital for surgical treatment of an intestinal obstruction. Her hemogram was within normal limits; the urine was also normal. Four months later toxic psychosis (paranoid psychosis) developed, with suicidal tendencies. There was also a moderately severe exacerbation of the lupus erythematosus, accompanied with convulsions and temperature elevation to 104 and 106 F. The patient refused further medication and died on the eighth hospital day. The blood count had consistently shown normal values.

CASE 5.—A. C., a Chinese woman aged 18, in May, 1947, had a deep red scaly macular eruption on the face and body. Two attacks followed a sunburn. The patient complained of malaise, fatigue, and fever. Arthralgia was present in the fingers and knee joint. Dr. H. Arnold Jr. believed the patient to be in a subacute phase of lupus erythematosus. The illness continued for several months with relapses and remissions.

On Aug. 10, 1947, she was admitted to The Queens Hospital with a sudden relapse of malaise, fever, and joint pains. A mottled purpuric rash appeared over the face and trunk. There was a positive reaction on the tourniquet test. The fever and general condition did not improve during the next nine days; therefore, the spleen was removed on Aug. 19, 1947.

The preoperative laboratory studies revealed 2,600,000 to 4,000,000 red blood cells and 4,800 white blood cells per cubic millimeter, with a normal differential count. The hemoglobin concentration was 11 gm. per 100 cc. of blood. The thrombocyte count was 185,000 per cubic millimeter. Prothrombin time was 33.3 seconds, and clot retraction time, 3 minutes 10 seconds. Cholesterol measured 84 mg. per 100 cc. of blood. The sedimentation rate was 37 mm. in one hour. Thymol flocculation was 9 units. Blood bilirubin was 6 mg. per 100 cc. Serum protein totaled 7.7 gm. per 100 cc.

Her postoperative course was uneventful, with a decided improvement in the outstanding complaints of fever, joint pains, and skin lesions. She was discharged from the hospital on the 10th postoperative day.

Four days after operation the laboratory studies had shown 4,000,000 red blood cells and 13,000 white blood cells per cubic millimeter, with 95% polymorphonuclear leucocytes and 5% lymphocytes. There was 11 gm. of hemoglobin per 100 cc. of blood. Cholesterol measured 135 mg. The sedimentation rate was 57 mm. in one hour.

Dr. McArthur, from the island of Maui, furnished me the following history of the patient after her discharge from the hospital. She experienced lassitude, malaise, and edema of the feet, legs, face, and hands. Her blood pressure increased to 180/110. All skin lesions regressed during the last two or three months.

Eight months after the operation the results of laboratory studies were as follows: Red blood cells numbered 1,750,000, and white blood cells, 10,200, per cubic millimeter, with 40% polymorphonuclear leucocytes, 26% stab forms, 32% lymphocytes, and 2% monocytes. The hemoglobin concentration was 4.5 gm. per 100 cc. The clotting time was 11 minutes, and the bleeding time, 3½ minutes. Urinalysis revealed 4+ red blood cells, white blood cells, and many granular casts. The sedimentation rate was 58 mm. in one hour. Creatinine measured 3.6 gm. per 100 cc. of blood. Serum protein totaled 4.6 gm. per 100 cc.

The nephritis and nephrosis progressed until the patient went into convulsive seizures resulting in her death, eight months after splenectomy.

Case 6.—M. N., a Japanese schoolgirl aged 17, received a severe sunburn at the beach. Within four days she noted a faint blush and macular eruption of the face. The patient complained of increasing joint pains, muscular ache, and general malaise. Her temperature began to spike to 104 F. She was hospitalized on Nov. 19, 1947, for a possible splenectomy.

The following preoperative laboratory data were obtained: Red blood cells numbered 3,350,000, and white blood cells, 3,900 to 5,400, per cubic millimeter, with a normal differential count. The hemoglobin concentration was 8.5 gm. per 100 cc. of blood. The thrombocyte count was 355,000 per cubic millimeter. Urinalysis revealed a normal condition. Cholesterol measured 62 mg. per 100 cc.

Splenectomy was performed because the patient became severely ill of the intensification of her systemic disease. Her postoperative course was uneventful, except for pleural effusion necessitating thoracentesis. Her postoperative recovery was dramatic. The cutaneous lesions disappeared completely; the temperature returned to normal, and the arthralgia and muscle tenderness subsided.

Postoperative laboratory studies showed 11.6 gm. of hemoglobin per 100 cc. of blood. Red blood cells were 4,130,000, and white blood cells, 12,100, per cubic millimeter, with 84% polymorphonuclear leucocytes; 14% lymphocytes, and 2% monocytes. The thrombocyte count was 539,000 per cubic millimeter. Urinalysis revealed albumin (4+) and occasional white and red blood cells.

She became cheerful, gained in weight, and was discharged from the hospital one month postoperatively. She returned to highschool in 30 days to continue a full course of studies during the next three months.

On March 29, 1948, she was readmitted to the hospital because of malaise and fever. Her face had become flushed and edematous as a result of relapse of the systemic lupus erythematosus. The attack subsided within three days, and her condition remained normal for the next six months.

Laboratory studies during the next six months showed normal white and red blood cell counts. The sedimentation rate remained increased at 26 mm. in one hour. Urinalysis revealed the presence of albumin (4+) and many white and red blood cells. The patient gained 20 lb. (9.1 kg.) and remained in good health until Oct., 1948. Then she experienced an evening rise in temperature to 102 F. and lassitude and lower back pain caused by severe nephritis and nephrosis that inexorably progressed during the last year. The face and extremities became increasingly edematous. The patient had a series of uremic convulsions and died on Dec. 24, 1948.

Case 7.—H. T., a Japanese housewife aged 23, gave birth to a viable premature baby on Dec. 18, 1947. During the last months of pregnancy, a rash had appeared on her face. In Dec. 1947, she was readmitted to the hospital because of a sudden flare-up of fever (temperature elevation to 101 to 103 F.), with chills and malaise. The facial lesions were over the malar areas and were edematous. Tender white-centered petechiae appeared on the fingertips. Severe polyarthralgia produced considerable distress. She became apathetic and emotional because her mother had died of acute systemic lupus erythematosus two years previously. The patient's temperature rose to 106 F., and she became critically ill.

Preoperative laboratory studies showed 3,100,000 red blood cells and 6,250 to 3,200 white blood cells per cubic millimeter, with 75% polymorphonuclear leucocytes, 2% stab forms, 21%

lymphocytes, and 2% eosinophiles. The hemoglobin concentration was 11 to 10.6 gm. per 100 cc. The thrombocyte count was 172,000 per cubic millimeter. The sedimentation rate was 36 mm. in one hour. Cholesterol measured 87 mg. per 100 cc. of blood. Urinalysis revealed many red and white blood cells and a 3+ reaction for albumin.

Splenectomy was performed by Dr. Sakimoto on Jan. 9, 1948, as a desperate measure. Within 48 hours, the lupus erythematosus was improved; then her condition went downhill.

Laboratory studies after the operation showed 4,680,000 red blood cells and 31,900 white blood cells per cubic millimeter, with 92% polymorphonuclear leucocytes and 8% lymphocytes. The hemoglobin concentration was 12.6 gm. per 100 cc. Urinalysis revealed albumin (4+) and many red and white blood cells.

The patient died five days postoperatively.

CASE 8.—E. W., a Chinese housewife aged 38, was hospitalized on May 13, 1948, because of temperature elevation to 101 to 105 F., chills, and malaise. She had been treated by a naturopath or osteopath for polyarthritis. During the short hospital stay, the patient displayed an erythematous macular blush and exanthem on the face and neck and complained of stiffness and tenderness of the muscles of the back and legs.

The laboratory studies showed 3,030,000 to 4,440,000 red blood cells and 3,850 to 4,250 white blood cells per cubic millimeter, with 92% polymorphonuclear leucocytes and 8% lymphocytes. There was 6.1 gm. of hemoglobin per 100 cc. of blood. The thrombocyte count was 129,000 per cubic millimeter. Sedimentation rate was 39 mm. in one hour. A culture of the blood was negative for pathogens. Urinalysis revealed a 1+ reaction for albumin and the presence of several white and red blood cells with granular casts.

The patient's course in the hospital became critical; she was semistuporous for several days.

Splenectomy was performed on May 22, 1948. Her postoperative course was stormy for three days. The rash faded considerably, and her condition appeared to improve temporarily, but she finally lapsed into coma.

Spiking fever continued, with temperature elevation to between 100 and 105 F. The hemogram, three days after the operation, revealed 2,800,000 red blood cells and 5,500 white blood cells per cubic millimeter, with 80% polymorphonuclear leucocytes and 20% lymphocytes. The hemoglobin concentration was 8.8 gm. per 100 cc. of blood. The thrombocyte count was 127,000. Nonprotein nitrogen measured 72 mg., and creatinine, 2.4 mg., per 100 cc. of blood.

The patient died on the ninth postoperative day.

CASE 9.—Y. T., a Japanese schoolgirl aged 16, first noted lassitude, joint pains, and chills in 1949. She was hospitalized for six months because of an exacerbation of her illness and generalized macular rash. The patient had lost 30 lb. (13.6 kg.) in body weight within the last year.

The laboratory studies revealed 3,130,000 red blood cells and 2,600 to 3,900 white blood cells per cubic millimeter, with 60% polymorphonuclear leucocytes, 15% lymphocytes, 24% stab forms, and 1% eosinophiles. The hemoglobin concentration was 7.5 to 11 gm. per 100 cc. of blood. Protein totaled 8.43 gm. per 100 cc., with 3.73 gm. of albumin and 4.7 gm. of globulin.

Dr. Thomas Fujiwara saw this patient at the Hilo Hospital, Hilo, T. H., and his sternal marrow examination revealed the presence of L. E. cells. The patient was sent to Honolulu for splenectomy to improve the granulocytopenia. She was given general supportive therapy, including several transfusions of whole blood. The eruption increased over the face and neck. Her condition appeared to be deteriorating rapidly.

Splenectomy was performed by Dr. John Devereux on May 14, 1950. The postoperative course was uneventful except for five days of temperature elevation to about 103 F. The "butterfly" malar eruption faded considerably. Two days following the operation, her hemogram showed 4,220,000 red blood cells and 8,200 to 11,000 white blood cells per cubic millimeter, with 72% polymorphonuclear leucocytes, 5% lymphocytes, 22% stab forms, and 3% basophiles. There was 10.5 to 11.5 gm. of hemoglobin per 100 cc. of blood. Urinalysis revealed a trace of albumin and several white blood cells. The patient was discharged from the hospital, afebrile and fairly comfortable, except for general weakness.

There was a two-month period of benefit. The patient began to fail and died three months postoperatively.

CASE 10.—R. K., a Japanese girl aged 16, had been ill for three months. She complained of edema of the face and ankles, weakness, malaise, and a pinpoint rash of the face. The patient

was hospitalized by Dr. Beck and Dr. H. Arnold Jr. on Sept. 7, 1950, because of acute nephritis secondary to lupus erythematosus. There were gross albuminuria, hematuria, pyuria, and hypoproteinemia. The skin lesions of lupus erythematosus appeared on the face, associated with pancytopenia including thrombocytopenia.

The laboratory studies revealed 3,100,000 red blood cells and 1,900 to 3,600 white blood cells per cubic millimeter, with a fairly normal differential count. The hemoglobin concentration was 8.5 gm. per 100 cc. The thrombocyte count ranged from 37,620 to 75,240. The Weltmann coagulation band was 8. Nonprotein nitrogen measured 55 mg., and creatinine, 1.7 mg., per 100 cc. of blood. Urinalysis revealed the presence of albumin (4+), white and red blood cells, and granular casts. Serum albumin was 2.02 gm., and serum globulin, 1.98 gm., per 100 cc. A positive reaction was obtained on the L. E. phenomenon test.

Splenectomy was performed on Sept. 20, 1950, the patient being classified as a poor surgical risk. The white blood cell and thrombocyte counts promptly rose to above-normal levels. The nosebleed ceased, but the patient remained toxic. There was an increase of fluid and sodium retention as manifested by generalized edema, and the urine output diminished rapidly. Pulmonary edema increased, and azotemia soared. The patient died on the seventh postoperative day in a uremic state, despite large doses of cortisone and corticotropin.

Case 11.—M. M., a Spanish-Arabian woman aged 31, had polyarthralgia in July, 1949. She complained of chest pain, dyspnea, and abdominal swelling. The patient was admitted to St. Francis Hospital with a flare-up of joint pains, malaise, weakness, fever, and facial erythema. The diagnosis of systemic lupus erythematosus was suggested on the basis of these signs. Her lesions gradually became acute and the chest pain unbearable.

The laboratory data were as follows: Red blood cells numbered 3,300,000, and white blood cells, 2,600 to 5,000, per cubic millimeter, with a normal differential count. The hemoglobin concentration was 5.5 gm. per 100 cc. of blood. The thrombocyte count was 180,000 per cubic millimeter. Urinalysis showed only a 4+ reaction for albumin.

The spleen was removed on April 18, 1950, as a measure of desperation. The postoperative course was serious for two weeks, but she gradually recovered. All symptoms of her disease subsided except the chest pain.

Within 24 hours after operation, the white blood cell count rose to 12,500; the red blood cell count and hemoglobin concentration remained the same. Three weeks later the blood count showed 9,400 white cells and a normal differential count. The red blood cells numbered 3,220,000. The hemoglobin concentration was 66%. Results of urinalysis were within normal limits.

During the next two years she was frequently hospitalized with pleural effusion, arthralgia, chest pain, and dyspnea. There was a remarkable change for the better in the general picture, but it could be attributed only to the use of corticotropin and cortisone.

Throughout 1952 her hemogram stayed within normal limits. The nonprotein nitrogen varied between 47.5 and 34 mg. per 100 cc. The sedimentation rate was 39 mm. in one hour.

Case 12.—L. K., a part-Hawaiian housewife aged 30, had had recurrent episodes of polyarthritis since 1948. In Sept., 1950, a series of attacks of chills, low-grade fever, polyarthritis, weakness, and cyanosis began, with pronounced weight loss. She was hospitalized with the diagnosis of rheumatic fever, but the diagnosis was changed to systemic lupus erythematosus after development of an erythematous malar flush. The laboratory findings were compatible with this disease, the tests showing anemia, leucopenia, negative result on blood culture, and presence of the L. E. phenomenon. The sedimentation rate was 41 mm. in one hour.

Her treatment consisted of repeated courses of corticotropin and cortisone administered from Oct., 1950, to May 1, 1951. There was a prompt relapse of her symptoms when corticotropin therapy was discontinued.

Splenectomy was performed on April 29, 1951, only as a possible aid in prolonging the remission. The patient received minimal benefit from the splenectomy, as the complaints remained the same. Her hemogram did not vary appreciably. The L. E. phenomenon was present for six weeks postoperatively.

In the last year and a half since the operation, she has been hospitalized repeatedly because of malaise, pains in finger joints, and slight fever. Drug addiction has developed from the prolonged usage of meperidine hydrochloride.

At present, the patient receives corticotropin and estrogenic hormones daily and has gained 20 lb. (9.1 kg.) in weight. She has obtained a full-time job, returning to Dr. T. Mossman for periodic corticotropin and general supportive therapy. The hematologic picture has not varied but has remained within normal limits.

BONE MARROW STUDIES

Bone marrow studies are important in the diagnosis of hypersplenism. The surgeon should be certain that the patient is able to produce enough cells from the marrow to maintain a normal cellular level. Without this prior knowledge, the result may be disastrous. The marrow in thrombocytopenic purpura should show an abundance of megakaryocytes, and in splenic neutropenia granulopoiesis should be present,[12] before splenectomy is undertaken.

The examination of aspirated sternal marrow in Cases 1 and 2 revealed moderate hyperplasia, with an increased activity of both the erythrocytic and the granulocytic series. There was an increase in the number of megakaryocytes, a majority of which were immature. The findings were compatible with the general picture of idiopathic thrombocytopenic purpura. In the other cases the sternal marrow was considered to be normoplastic, with a normal myeloid-erythroid ratio. The megakaryocytes were usually normal in number and mature in form.

SPLENIC LESIONS

In the pathologic study of hypersplenism, the spleen should be examined for changes in the structure of the vascular bed, in reticulum mesh, and its cellular components, in the lymphoid follicles and their reticulum, and in the free cells.[10] Recently, Leffler [13] reported on a series of 87 cases of hypersplenic pathology. He noted a prominent widened marginal zone of medium and large lymphocytes at the periphery of the Malpighian follicles. Two hundred twenty-four spleens from patients with diverse diseases other than hypersplenism were examined microscopically, but only 5.8% of the spleens showed prominent marginal zones. Klemperer and associates [14] were of the opinion that periarterial fibrosis is seen almost constantly in the spleen of lupus erythematosus and that it might be a specific sign. Kaiser [15] observed periarterial sclerosis in diverse diseases, as well as in acute systemic lupus erythematosus. This observation was substantiated by Baggenstoss,[16] but he felt that when periarterial sclerosis is present it is helpful in making a diagnosis.

The microscopic sections from 10 of the spleens removed in this series showed concentric periarteriolar collagen lamination ("onion peeling"). Twelve spleens presented sinus hyperplasia (actually fibrosis and increased cellularity of the intersinusoidal tissue of the red pulp, allowing numerous sinus spaces to be seen). Ten

12. Welch, C. S., and Dameshek, W.: Splenectomy in Blood Dyscrasias, New England J. Med. **242**:601-606 (April 20) 1950.

13. Leffler, R. J.: The Spleen in Hypersplenism, Am. J. Path. **28**:303-313 (March-April) 1952.

14. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569-631 (Oct.) 1941.

15. Kaiser, I. H.: The Specificity of Periarterial Fibrosis of the Spleen in Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **71**:31-41 (July) 1942.

16. Baggenstoss, A. H.: Visceral Lesions in Disseminated Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **27**:412-419 (Oct. 22) 1952.

spleens showed the Malpighian corpuscular marginal zone as described by Leffler.[13] Eight of the spleens were moderately enlarged, and four spleens were normal in size and weight.

COMMENT

The problem of lupus erythematosus is of considerable interest in Hawaii. Undoubtedly, the L. E.-cell phenomenon has aided many physicians in classifying the disease as systemic lupus erythematosus. I am convinced that the incidence of lupus erythematosus in Hawaii is equal to, or possibly greater than, that in other areas of the world. The highest number of cases are seen in Japanese and Chinese persons. Solar radiation may be another factor, but is not any more important than in Florida or California. Sunburn precipitated the disease in three of the cases presented. Montgomery and McCreight [17] reported that 32 cases were seen at the Mayo Clinic from 1938 to 1947. Forty-four cases were reported in hospitals in Honolulu over a six-year period.

There have been isolated reports in the literature of removal of the spleen because of some disease other than systemic lupus erythematosus, with development at a later date of the classic changes of acute lupus erythematosus. Hargraves [18] observed the development of acute systemic lupus erythematosus in three patients who underwent splenectomy for hypersplenism. One of the patients died 10 months after splenectomy. The other two are still alive. Costello, in the discussion on Montgomery's paper,[17] stated that he had seen a patient splenectomized in 1945 because of thrombocytopenic purpura, in whom dermatitis herpetiformis developed and progressed to acute systemic lupus erythematosus, with death due to Stevens-Johnson syndrome. An accessory spleen was found at autopsy. This may have been the tissue that reactivated the hypersplenism. Keil [2] reported, in 1937, on an unusual patient with thrombocytopenic purpura that necessitated splenectomy, who subsequently died of acute systemic lupus erythematosus. Wise [1] had a similar patient, who died of renal insufficiency. Similar cases have been reported in the past. It is probable that in many of these cases the thrombocytopenia was merely the initial manifestation of systemic lupus erythematosus.

The changes in the hemogram in acute systemic lupus erythematosus have been known for a long time. At times, the peripheral blood may show striking depressions of the formed elements. Granulocytopenia represents a most important feature of lupus erythematosus and ultimately predisposes to death. Michael and his group [19] reported that 59% of their series had a white blood cell count of 5,000 or less. Coburn and Moore [20] reported that all their patients had leucopenia. Anemia is a common feature in such patients; some may not show evidence of anemia in the early phase of the disease, but the degree of anemia seems to be dependent on the

17. Montgomery, H., and McCreight, W. G.: Disseminate Lupus Erythematosus, Arch. Dermat. & Syph. **60**:356-372 (Sept.) 1949.

18. Hargraves, M. M.: The L. E. Cell Phenomenon, Proc. Staff Meet., Mayo Clin. **27**:419-423 (Oct. 22) 1952.

19. Michael, S. R.; Vural, I. L.; Bassen, F. A., and Schaefer, L.: The Hematologic Aspects of Disseminated (Systemic) Lupus Erythematosus, Blood **6**:1059-1072 (Nov.) 1951.

20. Coburn, A. F., and Moore, D. H.: The Plasma Proteins in Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **73**:196-221 (Sept.) 1943.

duration and severity of the illness. Dubois [21] reported in 1952 on three cases of acquired hemolytic anemia associated with acute systemic lupus erythematosus. He believed the anemia could be based on hypersplenism. Thrombocytopenia occurs frequently, but the thrombocyte count is occasionally overlooked on hemogram studies. Coburn and Moore [20] reported that 23% of their series had thrombocytopenic purpura. Michael and associates [19] observed that 39% of all patients manifested thrombocytopenic purpura at some time during their illness.

Brady and Neal [22] reported on a patient who underwent splenectomy in systemic lupus erythematosus with thrombocytopenic purpura. The hemogram showed a marked depression of the formed elements. Generalized purpura occurred. In desperation, splenectomy was performed, as the patient appeared moribund at that time. Three months postoperatively, the thrombocyte count had risen to 80,400 per cubic millimeter and the general hemogram and condition of the patient had improved considerably. During the first year after the operation, the patient gained 30 lb. in weight and the general appearance was excellent. This patient survived two and a half years and died of the primary disease. In most of the scattered reports in the literature, the patients were splenectomized for thrombocytopenia, with subsequent development of lupus erythematosus. Thrombocytopenia may be one of the earlier peripheral blood findings, before the changes of the more classic form of systemic lupus erythematosus are evident. The spleen is not always the major organ in thrombocytopenia. Harrington and his group [23] found a thrombocytopenic factor in the blood of 8 of 10 patients with thrombocytopenic purpura. Transfusions of plasma or whole blood from nine of these patients to healthy recipients produced a sudden drop in the thrombocyte level. Two of the recipients subsequently manifested characteristic hemorrhages of thrombocytopenic purpura. Harrington stated that the circulating thrombocytopenic factor was fairly stable, and that it is a plasma constituent present in the globulin fraction.

Kracke and Risler [24] stated that if a disease is accompanied with hypersplenism to the degree that the patient becomes anemic, thrombocytopenic, and leucopenic, splenectomy should be considered as a helpful or palliative measure.

It was with this in mind that splenectomy was performed on patients of this series. These 12 patients had leucopenia and moderate to severe anemia preoperatively. Thrombocytopenia was noted in four (33%). Two (Cases 1 and 2) presented severe thrombocytopenic purpura, leucopenia, and anemia. Splenectomy was considered to improve the hematologic picture.[12] Both patients were bleeding from all orifices of the body and were practically moribund at the time of surgery. The dramatic clinical improvement, as well as the hematologic change, prompted further investigation in other cases of systemic lupus erythematosus. Nine patients were classed preoperatively as in critical condition and were not expected to live.

21. Dubois, E. L.: Acquired Hemolytic Anemia as the Presenting Syndrome of Lupus Erythematosus Disseminatus, Am. J. Med. **12**:197-203 (Feb.) 1952.

22. Brady, J. H., and Neal, W. S.: Splenectomy in a Case of Disseminated Lupus Erythematosus with Thrombocytopenic Purpura, California Med. **28**:448-449 (June) 1948.

23. Harrington, W. J.; Minnich, V.; Hollingsworth, J. W., and Moore, C. V.: Demonstration of Thrombocytopenic Factor in Blood of Patients with Thrombocytopenic Purpura, J. Lab. & Clin. Med. **38**:1-10 (July) 1951.

24. Kracke, R. R., and Risler, W. H., Jr.: The Problem of Hypersplenism, J. A. M. A. **141**:1132-1139 (Dec. 7) 1949.

Two patients were classed as in fair condition, and one (Case 11) was a satisfactory risk. Three patients died within nine days postoperatively, and the others lived three months to seven years.

Three patients are still living. All the patients except three showed relief of symptoms and signs of fever, arthralgia, malaise, and skin lesions. Two (Cases 11 and 12) are kept asymptomatic with periodic cortisone and corticotropin therapy. The hemograms were improved in all the patients, sometimes dramatically.

For some time splenectomy in certain diseases has been known to improve the peripheral blood picture and maintain a normal blood count for months to years. Systemic lupus erythematosus is one of these diseases, although, unfortunately, the primary disease usually progresses inexorably. Splenectomy is not the solution to the problem of this obscure disease, but it can indicate a link in the chain of events. In the occasional case with hypersplenism, splenectomy has been a life-saving or palliative measure.

SUMMARY AND CONCLUSIONS

Recent work has attempted to define the physiology of the normal spleen. The relation of altered physiology to the commonly accepted hypersplenic syndromes and to some conditions not thus commonly classified has been studied. There is increasing consideration of hypersplenism as an exaggeration of one or more of the normal functions of the spleen, thereby producing a pathologic state.

The results of 12 splenectomies performed on patients acutely ill of systemic lupus erythematosus are presented. In the first two, the disease was complicated by thrombocytopenia, and response to splenectomy was dramatic. The other patients showed favorable clinical and hematological changes.

Splenectomy may usually be relied on permanently to eliminate thrombocytopenia, leucopenia, or acquired hemolytic anemia from the clinical picture of systemic lupus erythematosus. The procedure is indicated when any of these manifestations are present and sufficiently severe to threaten the patient's well-being.

Splenectomy may be followed by a remission of systemic lupus erythematosus; however, this may be no more than a temporary improvement.

ABSTRACT OF DISCUSSION

Dr. Louis A. Brunsting, Rochester, Minn.: This series of patients in whom splenectomy was performed in acute systemic lupus erythematosus is by far the largest reported. The operation represents a courageous attempt to interrupt the progressive decline of the patient with certain symptoms manifesting an abnormality of the hemopoietic system. Neutropenia and thrombocytopenia are almost constant findings in systemic lupus erythematosus, as they are in another group of diseases, typhoid, malaria, measles, and influenza, which are infectious disorders and in which the abnormalities in the blood picture are not necessarily vital.

The removal of the spleen in systemic lupus erythematosus, with its hematologic repercussions, means relatively little so far as the disease itself is concerned but is of great interest as regards the leucopenia. The rise in the blood counts following splenectomy confirms the belief that functioning hypersplenism accounts for the suppression of the leucocytes and the thrombocytes in this disease, as it does in the other diseases mentioned. Dr. Johnson states that granulocytopenia predisposes to the death of patients with lupus erythematosus. This statement is controversial. Actually there is no abnormality of the clotting mechanism in this disease; rather, the hemorrhagic lesions that occur are vascular in origin. There is no counterpart in lupus erythematosus to the ulcerative lesions that occur in true agranulocytosis. On the other hand, hemolytic crises may, and frequently do, occur and contribute to the death of the patient.

Analysis of the protocols submitted indicates that splenectomy is a futile attempt at altering the course of systemic lupus erythematosus. In reviewing the sequence of events in the 12 cases summarized, one is impressed, as usual, by the high incidence of deaths due to renal disease. Truly, the state of renal function in these patients is an index to the prognosis. Of the three patients who are living, in one (Case 1) splenectomy was performed at the age of 37 and the patient is now 44 years of age. At this age in women, the disease naturally runs a milder course. Two patients (Cases 11 and 12) are being maintained on hormone therapy. In one (Case 12) it is stated that the urine is normal, and it is assumed that the same obtains in the other two. The sex and age of the patient and the state of renal function are prime factors in the prognosis of systemic lupus erythematosus. Other instances reported in the literature of splenectomy in lupus erythematosus, as well as the cases in my experience, confirm the fact that the earliest symptoms of the disease may indicate some hematologic abnormality. Even though splenectomy is performed, other well-known manifestations of the disease become evident sooner or later and the eventual course is unaltered. Obviously, splenectomy is not the answer to the control of systemic lupus erythematosus.

DR. SAMUEL M. PECK, New York: I have been following the results of splenectomy in acute lupus erythematosus with a great deal of interest, but from another point of view.

Before the advent of the serologic diagnosis of acute systemic lupus erythematosus my associates and I attempted to differentiate the acute systemic form from the chronic discoid form by using the moccasin-venom test. We found that the test (*Proc. Soc. Exper. Biol. & Med.* **35**: 614-616, 1937) gave a negative result in discoid lupus erythematosus, but a positive result in some cases of subacute and in nearly all cases of acute systemic lupus erythematosus.

The role of splenectomy in its effects on the course of acute lupus erythematosus has perhaps another basis.

Dr. Nathan Rosenthal and I followed a great many cases of thrombocytopenic purpura with the venom test (*J. A. M. A.* **106**:1783-1791, 1936) before and after splenectomy. We noted that in nearly every case the venom reaction was positive before the operation and became negative after the operation, sometimes as quickly as three hours postoperatively.

Clinically, the patients usually stopped bleeding shortly after splenectomy, practically at the same time that the reaction became negative. This occurred before the thrombocytes had time to regenerate.

Our interpretation of this phenomenon was that the spleen produced a capillary toxic factor. With the removal of the source of supply for this capillary toxin, the bleeding was diminished and the venom reaction became negative.

This leads me to speculate that perhaps the spleen produces a toxic factor which plays a role not only in thrombocytopenic purpura, but in acute systemic lupus erythematosus. In both conditions splenectomy removes a related etiologic agent or agents.

DR. HAROLD M. JOHNSON, Honolulu, T. H.: The concept of the spleen as a gland of internal secretion has developed gradually during the last quarter of a century. Recent evidence suggests a relation between the gland system and the process of hemopoiesis.

Dr. P. E. Smith noted a progressive decrease in the size of the spleen and its return to normal proportions if pituitary homotransplants were made in hypophysectomized adult rats (*Am. J. Anat.* **45**:205, 1930). Injections of pituitary extracts will also produce a progressive hypertrophy of the spleen.

Steinberg recently (*Ann. Int. Med.* **38**:787, 1953) suggested that the reason splenectomy is helpful in similar syndromes is that a marked secondary hypertrophy of the anterior pituitary body occurs, producing a constant release of corticotropin, thus giving the beneficial effect.

Splenectomy in lupus erythematosus occasionally is imperative to prevent fatal blood loss or damage to the brain, kidney, and other vital structures. I wish to emphasize that this report does not advocate indiscriminate use of splenectomy. Each case should be carefully evaluated and the procedure properly confined to a small group of selected cases.

Dr. Thomas H. Fujiwara studied the sternal bone marrow aspirates.

Dr. H. Civin examined the histologic sections of the spleens.

EFFECT OF CORTISONE AND CORTICOTROPIN ON PROGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Survey of Eighty-Three Patients with Positive Plasma L. E. Tests

JOHN R. HASERICK, M.D.
CLEVELAND

SYSTEMIC lupus erythematosus was among the first diseases treated with cortisone and corticotropin. In many cases striking benefit has been reported.[1] The merit of prolonged use of steroid preparations in a maintenance program is now under evaluation.[2] Despite these apparent advances in treatment, patients still die from the disease. The imminent question is: How many live and for how long because of steroid therapy? (The term steroids will be used here to indicate cortisone, hydrocortisone acetate, and corticotropin.)

A study of the present day prognosis of systemic lupus erythematosus must include a comparison with the natural course of the disease before steroids were introduced. Superficially this would appear to be an easy task. Actually, owing to the broad nature of systemic lupus erythematosus, there are many difficulties. For example, no classification of lupus erythematosus has ever been universally accepted. The term disseminated means a scattering of skin lesions to some but systemic involvement to others. Similarly, "acute" may indicate either severity or short duration of the disease. Thus, previous studies on the natural course of systemic lupus erythematosus, based only upon clinical impressions, present a difficult problem in variables.

Read before the Seventy-Third Annual Meeting of the American Dermatological Association, Lake Placid, New York, June 9, 1953.

From the Department of Dermatology, Cleveland Clinic (Earl W. Netherton, M.D., Chief), and the Frank E. Bunts Educational Institute.

This investigation was supported in part by a research grant from the National Institutes of Health, United States Public Health Service.

1. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions: Study in Clinical Physiology, Arch. Int. Med. **85**:545, 1950. Baehr, G., and Soffer, L. J.: Treatment of Disseminated Lupus Erythematosus with Cortisone and Adrenocorticotropin, Bull. New York Acad. Med. **26**:229, 1950. Soffer, L. J.; Levitt, M. F., and Baehr, G.: Use of Cortisone and Adrenocorticotropic Hormone in Acute Disseminated Lupus Erythematosus, Arch. Int. Med. **86**:558, 1950. Brunsting, L. A.; Slocumb, C. H., and Didcoct, J. W.: Effects of Cortisone on Acute Disseminated Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **25**:479, 1950; Effects of Cortisone on Acute Disseminated Lupus Erythematosus, A. M. A. Arch. Dermat. & Syph. **63**:29, 1951.

2. (*a*) Dubois, E. L.; Commons, R. R.; Starr, P.; Stein, C. S., Jr., and Morrison, R.: Corticotropin and Cortisone Treatment for Systemic Lupus Erythematosus, J. A. M. A. **149**:995, 1952. (*b*) Soffer, L. J., and Bader, R.: Corticotropin and Cortisone in Acute Disseminated Lupus Erythematosus: Results of Long-Term Use, ibid. **149**:1002, 1952.

Recognition of the L. E. phenomenon provided a sheet anchor for the diagnosis of systemic lupus erythematosus and thereby a consistent basis for comparison. L. E. tests, based upon the demonstration of the L. E. phenomenon, have supplied much the same sort of orientation for systemic lupus erythematosus that the discovery of the specific serologic tests provided for syphilis. L. E. tests are found to be positive in nearly all cases of severe systemic lupus erythematosus. Moreover, L. E. tests have aided materially in detecting the milder atypical forms of the disease, furthering an appreciation of its widespread protean nature.[3] Conversely, certain so-called "typical" cases of systemic lupus erythematosus, in which negative L. E. tests seemed at the time disconcerting and irreconcilable, have often in final diagnosis been established not as lupus erythematosus but as entirely unrelated diseases. Cases of trichiniasis have been seen in which the diagnosis at admission was systemic lupus erythematosus. Last fall, a 17-year-old girl was admitted to the hospital with a working diagnosis of systemic lupus erythematosus. She was acutely ill, with a high fever and a "butterfly" erythema. The result of the plasma L. E. test was negative. Within a week every symptom had disappeared. The final diagnosis was dermatitis medicamentosa, with penicillin as the etiologic agent. The patient has continued to remain well. Such experiences present a direct challenge to statistics based only upon clinical impressions of systemic lupus erythematosus without the use of L. E. tests.

PLASMA L. E. TEST

The present report comprises only cases in which diagnosis of systemic lupus erythematosus was associated with the presence of the Hargraves L. E. phenomenon.

Since February, 1949, the plasma L. E. test [4] has been employed routinely in the special hematology laboratory of the Cleveland Clinic. Based upon the in vitro production of the L. E. phenomenon,[5] the plasma L. E. test has the following advantages over L. E. tests which utilize the patient's own peripheral blood or bone marrow:

1. Only the in vitro plasma L. E. tests have controls. Known L. E. plasma and normal plasma preparations representing positive and negative standards are compared simultaneously with the unknown plasma.

2. The tests may be repeated without disturbing the patient, because the plasma remains available on refrigeration.

3. Plasma L. E. tests are more easily and quickly read because of the abundance of cells on the stained preparation.

4. Tests are quickly and easily run, for example, 20 in two hours on the average.

5. Plasma can be sent long distances for testing.

6. The procedure can be used as a research standard. For example, chemicals can be added to determine their effect on the L. E. factor. When hydrocortisone acetate or cortisone was added to L. E. plasma in vitro, no change was noted.

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3. Haserick, J. R.: Plasma L. E. Test in Systemic Lupus Erythematosus: Study of 23 Patients with Positive L. E. Tests, J. A. M. A. **146**:16, 1951.

4. Haserick, J. R., and Bortz, D. W.: A New Diagnostic Test for Acute Disseminated Lupus Erythematosus, Cleveland Clin. Quart. **16**:158, 1949.

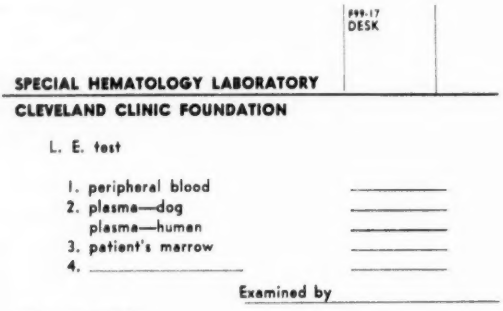
5. Haserick, J. R., and Bortz, D. W.: Normal Bone Marrow Inclusion Phenomena Induced by Lupus Erythematosus Plasma, J. Invest. Dermat. **13**:47, 1949.

7. Assistants in the Research Division aspirate the dog marrow, sparing the technicians of the special hematology laboratory the time and trouble of marrow preparation. (This is an advantage only in large institutions.)

In special cases a battery of L. E. tests will be carried out and reported on a laboratory report (Chart).

During 1951, a total of 1,048 plasma L. E. tests was reported from the special hematology laboratory. The total number of patients tested was 581. Positive plasma L. E. tests were found in 23 patients. In 1952, plasma L. E. tests numbering 1,338 were done on 755 patients, 26 of whom had positive L. E. tests. The total number of L. E. tests done by the in vitro technique from 1949 to April, 1953, was 3,700. The plasma from 83 clinic patients and 52 outside patients has been found to induce positive plasma L. E. tests.

The present report is concerned with the 83 personally observed patients in whom the clinical diagnosis of systemic lupus erythematosus was supported by one or more positive plasma L. E. tests. For purposes of comparison, the patients are divided



Laboratory report form used for L. E. tests.

according to the date of the first positive L. E. test. Thus, 10 patients were seen in the 12-month interval between November, 1948, and November, 1949, i. e., before cortisone was available. Fifteen cases were diagnosed systemic lupus erythematosus, and the patients were treated between November, 1949, and November, 1950; 22 patients were treated for lupus erythematosus between November, 1950, and November, 1951, and 26 patients were treated similarly between November, 1951, and November, 1952. The remaining patients were seen between November, 1952, and April, 1953.

COURSE OF SYMPTOMATICALLY TREATED SYSTEMIC LUPUS ERYTHEMATOSUS

Pre-L. E. Test and Presteroid Studies.—In 1952, Dubois [2n] made a statistical survey of the duration of systemic lupus erythematosus from the first onset of symptoms until death in three series of patients. His findings are summarized in Table 1.

In Dubois' own series, a "spontaneous remission" was noted in "at least 20 per cent of the cases." In patients receiving "current treatment," presumably steroids, the spontaneous remission was "perhaps 40 per cent." No attempt was made to clarify the term spontaneous remission with respect to degree and permanence.

Jessar, Lamont-Havers, and Ragan [6] studied the duration and course of 44 patients over a 15-year period. In the absence of the L. E. test the diagnosis of systemic lupus erythematosus was based upon the following criteria, set up in 1948 by Brenner and co-workers [7]: erythematous skin lesions, constitutional symptoms, negative blood culture, arthralgia, renal disease, suppression of blood-forming elements, adenopathy, nonbacterial endocarditis, serous membrane effusion, and predilection for women. The diagnosis of systemic lupus erythematosus was made if 7 of 10 of the criteria were met. Of their 44 patients, 13 (30%) were alive more than five years after the initial diagnosis. Of 16 patients with an autopsy diagnosis of systemic lupus erythematosus, 3 (18%) had lived longer than five years.

Positive L. E. Test Group (Presteroid).—Because of the short interval of time between the discovery of plasma L. E. tests in February, 1949, and the use of steroids in the management of systemic lupus erythematosus in November, 1949, only 10 untreated positive L. E. test patients were available for study (Table 2). The group is presented not only because the clinical diagnosis was supported in each instance by a positive plasma L. E. test but also because the hospital records, incomplete even at best, were supplemented by personal knowledge of each patient. This was of particular importance in evaluating the severity of the illness, especially

TABLE 1.—*Duration of Untreated Systemic Lupus Erythematosus Terminating in Death**

No. of Patients	Median, Mo.	Arithmetic Mean, Mo.	Geometric Mean, Mo.
20 (Klemperer †)	9	23	13.3
26 (Tumulty [11])	..	52	....
34 ‡ (Dubois [28])	24	38.5	24.4

* From Dubois' studies. "Untreated" was used by Dubois to mean symptomatic treatment without steroids.

† Klemperer, P.; Pollack, A. D., and Baehr, G.: Arch. Path. **32**:569, 1941.

‡ Los Angeles County General Hospital series from 1935 to 1950.

in making clinical comparisons between the steroid-treated and symptomatically treated groups of patients.

The average of the total duration of illness in this group was two years and seven months. The one patient still living (Control 10) is in a complete laboratory and clinical remission five years after her last exacerbation. In April, 1953, the plasma L. E. test was negative. She was hospitalized for four months in 1948, receiving only supportive therapy. At several times during the hospitalization she was not expected to survive. Though the clinical manifestations did not appear until one year before the positive plasma L. E. test, the history of false positive serologic tests for syphilis suggests the existence of the lupus diathesis in 1944.[8] The false-positive nature of the serologic tests for syphilis in this patient was supported by a negative treponemal immobilization test, which was reported by Dr. Nelson, of Johns Hopkins University.

6. Jessar, R. A.; Lamont-Havers, R. W., and Ragan, C.: Natural History of Lupus Erythematosus Disseminatus, Ann. Int. Med. **38**:717, 1953.

7. Brenner, J. J.; Leff, W. A., and Hochstein, E.: Lupus Erythematosus Disseminatus Sine Lupo with the Nephrotic Syndrome, Am. J. Med. **5**:288, 1948.

8. Haserick, J. R., and Long, R.: Systemic Lupus Erythematosus Preceded by False-Positive Serologic Tests for Syphilis: Presentation of 5 Cases, Ann. Int. Med. **37**:559, 1952.

In a series of 10 "untreated" patients with systemic lupus erythematosus, for whom the clinical diagnosis was corroborated by positive plasma L. E. tests, only one (10%) survived five years after entering the serious phase of the disease. Controls 1 and 5 received steroid therapy in minimal doses during terminal stages, but not enough to warrant placing them with the steroid-treated group.

The duration of life after the first positive plasma L. E. test varied from one month to one year in the fatal cases. It is of interest to compare by year the groups of patients seen after the first use of steroids in November, 1949.

TABLE 2.—*Summary of Presteroid Positive L. E. Test for Systemic Lupus Erythematosus (Ten Patients)*

Control Case, No.	Sex	Age, Yr.	Date of Positive L. E. Test	Duration of Disease Before L. E. Test	Total Duration of Disease	Outcome	Remarks
1	F	28	4/11/49	1 yr.	2 yr.	Died	4 mo. remission
2	F	26	2/ 9/49	4 yr.	4 yr. 2 mo.	Died	.....
3	M	31	3/ 8/49	6 mo.	7 mo.	Died	Never acutely ill until final week
4	F	25	4/19/49	8 yr.	8 yr.	Died	.....
5	F	18	4/ 5/49	2 yr.	3 yr.	Died	.....
6	F	27	5/20/49	3 yr.	3 yr. 7 mo.	Died	.....
7	F	31	6/ 6/49	1 mo.	2 mo.	Died	Positive S. T. S.* 6 years
8	F	17	6/16/49	10 mo.	10 mo.	Died	.....
9	F	21	8/ 5/49	2 mo.	3 mo.	Died	.....
10	F	34	11/30/48†	1 yr.	5 yr.	Living and well	Negative L. E. test 1953

* S. T. S., serologic test for syphilis.
† Stored plasma tested in April, 1949.

TABLE 3.—*Deaths in Patients with Systemic Lupus Erythematosus Treated with Steroids (1950-1951)*

Case No.	Sex	Type of Death
1	F	Renal failure; remission of 1 yr. while on cortisone therapy
2	F	L. E. crisis; moribund on admission; died on 4th day of hospitalization
3	F	L. E. crisis; moribund on admission; died on 4th day of hospitalization
4	F	L. E. crisis after remission of 7 mo. while on cortisone therapy
5	F	Cortisone discontinued elsewhere; type of death unknown
6	F	Cortisone discontinued elsewhere; heart failure

SYSTEMIC LUPUS ERYTHEMATOSUS TREATED WITH STEROID THERAPY

November, 1949, to November, 1950.—Cortisone was first used at the Cleveland Clinic in November, 1949. During the following year 15 patients with positive plasma L. E. tests, for systemic lupus erythematosus were treated with cortisone. Six of these patients died within two years. Table 3 summarizes the types and causes of death in these cases.

Cases 1, 2, 3, and 4 were examples of severe systemic lupus erythematosus. In each case the disease was considered to be imminently fatal without steroid therapy. The patient of Case 1 was in uremia, with a blood urea of 231 mg. per 100 cc. and seemed moribund on her first admission to the hospital. After one week of cortisone therapy the blood urea dropped to normal, and a remission started, which lasted one year. The patients of Cases 2 and 3 were moribund on admission and did not respond to the usual doses of cortisone. The massive dose

technique[9] had not yet been developed. The danger of underestimating the less explosive type of systemic lupus erythematosus is exemplified in Cases 5 and 6. In these instances the disease was not considered to be of such serious portent. Their cortisone maintenance program was interrupted elsewhere. Exacerbation of the disease and death followed.

Eleven of the 15 patients were classified as having impendingly fatal lupus erythematosus. Seven are considered to be alive because of treatment with cortisone. Each patient responded promptly to the drug during the acute stages and was then carried on a prolonged uninterrupted maintenance program. Four of the 15 patients were not acutely ill when steroid therapy was started. Two of these patients (Cases 5 and 6) are dead. Two are still in remission.

TABLE 4.—*Deaths in Patients with Systemic Lupus Erythematosus Treated with Steroids (1950-1951)*

Case No.	Sex	Type of Death
7	F	2-yr. remission on steroids; fatal L. E. crisis after severe herpes zoster
8	F	Progressive renal failure; no response to steroids
9	F	2-yr. remission on steroids; fatal L. E. crisis; ruptured peptic ulcer (hydrocortisone acetate?)

TABLE 5.—*Deaths in Patients with Systemic Lupus Erythematosus Treated with Steroids (1951-1952)*

Case No.	Sex	Cause of Death
10	F	Progressive renal failure; no response to steroids
11	F	Progressive renal failure; no response to steroids
12	F	Heart failure; 6-mo. partial remission on steroids
13	F	Septicemia with unidentified fungus
14	F (1953)	Suicide in 6th week of corticotropin (ACTH)-induced remission

TABLE 6.—*Presteroid Summary (Ten Cases)*

Yr.	No. of Patients	Treated with Steroids	Fatal Outcome Expected	Steroids Rated Life-Saving	No. Living in 1953
1948-1949	10	0	10	0	1

TABLE 7.—*Poststeroid Summary (Seventy-Three Cases)*

Yr.	No. of Patients	Treated with Steroids	Fatal Outcome Expected	Steroids Rated Life-Saving	No. Living in 1953
1949-1950	15	15	11	7	9
1950-1951	22	22	15	12	19
1951-1952	27	25	13	8	22
1952	9	8	5	3	8
Totals	73	70	44	30	58

9. Haserick, J. R.; Corcoran, A. C., and Dustan, H. P.: ACTH and Cortisone in the Acute Crisis of Systemic Lupus Erythematosus, J. A. M. A. **146**:643, 1951.

Nine (60%) of the 15 patients are in remission in 1953. Six of the nine patients still require steroid therapy.

November, 1950, to November, 1951.—There were 22 patients with positive plasma L. E. tests for systemic lupus erythematosus during this period. Three died (Table 4).

Twelve other patients in this group of 22 had severe, potentially fatal systemic lupus erythematosus. All responded to cortisone and corticotropin during the acute stages and subsequently were placed upon a maintenance program. Four of this group had entered the acute lupus erythematosus crisis but responded to the massive dose technique. All 12 patients still required steroids in 1953.

Seven of the 22 patients were classified as having moderately severe systemic lupus erythematosus. A fatal outcome in any of these patients would have been unexpected. All are living in 1953. Steroid therapy could not be credited as being life-saving in any of these seven patients.

November, 1951, to November, 1952.—Twenty-seven cases were diagnosed as systemic lupus erythematosus during this period. Five patients died (Table 5).

Eight other patients with severe, presumably fatal systemic lupus erythematosus responded to steroid therapy. Fourteen patients with moderately severe systemic lupus erythematosus are also living in 1953. Steroid therapy was not considered to be a life-saving measure in these cases.

COMMENT

There are two principal end-points upon which the natural course of systemic lupus erythematosus can be compared with the course affected by steroid treatment. The first is the length of time between the onset of symptoms and death. This factor is the more difficult one to decide. As pointed out by Dubois,[10] the arithmetic mean in untreated systemic lupus erythematosus varied from 23 months in one series to 52 months in another. However, the use of the L. E. test has in one sense complicated the concept of the disease's prodrome. In Tumulty's original series of patients,[11] the disease, which was diagnosed without the use of L. E. tests, had an over-all duration of 52 months. Later, when the diagnosis of systemic lupus erythematosus was based upon L. E. tests, Tumulty[12] found that the length of time between the onset of symptoms and death had stretched to 90 months.

This lengthening of the duration of systemic lupus erythematosus when L. E. tests are used is a reflection not upon a change in the disease itself but upon the discovery through the L. E. tests of atypical, often subclinical forms.[3] This difference is apparent in the present study. In 1948-1949, when plasma L. E. tests were used merely to confirm or support the clinical diagnosis of systemic lupus erythematosus, 10 out of 10 patients were considered to have serious involvement, with potentially fatal disease (Table 6). Later, when the plasma L. E. tests were used freely for the detection of atypical cases, only 44 out of 73 patients were classified as having imminently fatal systemic lupus erythematosus (Table 7).

10. Dubois, E. L.: Systemic Lupus Erythematosus, M. Clin. North America **36**:1111, 1952.

11. Tumulty, P. A., and Harvey, A. M.: Clinical Course of Disseminated Lupus Erythematosus: Evaluation of Osler's Contributions, Bull. Johns Hopkins Hosp. **85**:47, 1949.

12. Tumulty, P.: Clinical Course of Lupus Erythematosus Disseminatus, Alpha Omega Alpha Lecture, Western Reserve University, Cleveland, April 30, 1953.

In comparing the first group of steroid-treated patients (1949-1950) with the nonsteroid-treated group (1948-1949) on the point of duration of life with this illness, it will be noted that 11 of the steroid-treated patients were considered to anticipate a rapidly fatal outcome. Seven of these patients are alive in 1953. Only 1 of the 10 untreated patients with a similar degree of illness lived longer than one year. Thus, steroid therapy used without interruption over a long period of time appears to have prolonged the life of a significant number of patients. Parenthetically, the dosage used to maintain the remissions varied according to the individual requirements of the patients from 10 units of corticotropin to 100 to 125 mg. of cortisone acetate per day.

The second end-point upon which a comparison can be drawn between the steroid-treated and the nonsteroid-treated patients with systemic lupus erythematosus is the interruption of a rapidly lethal course. The continued lives of 30 (68%) of the 44 patients considered to have immediately fatal systemic lupus erythematosus were attributed to the intervention of steroid therapy. Since these patients were still living in 1953, most had survived beyond the one year noted previously in the fatal cases of the control group.

An analysis of the causes of death reveals 14 patients in whom steroid treatment was unsuccessful. In four of these patients renal failure was progressive, despite steroid therapy. A few patients died in L. E. crisis identical to that of presteroid days. One patient died from a septicemia with an unidentified fungus. At postmortem examination, abscesses composed mostly of mycelia were found in nearly every organ. Two patients (Cases 9 and 15) died from complications commonly considered to be induced by steroid therapy. In Case 9, death followed a perforated peptic ulcer and peritonitis. One patient (Case 15) had schizophrenia and committed suicide during the sixth week of a corticotropin-induced remission. At autopsy there was no evidence of systemic lupus erythematosus in any tissue.

Not stressed in the statistics as presented is a frequently noted improvement in morbidity. One patient, accustomed to three or four attacks of pneumonitis a year, has not been ill during three years of a cortisone-induced remission. Another patient, bedridden for two years prior to steroid therapy, has been working for two years.

In 1951, a young woman with classic "acute disseminated" lupus erythematosus became pregnant seven months after cortisone therapy was started. After a full-term gestation, during which time the cortisone acetate requirement varied between 75 and 150 mg. per day and 10 units per day of corticotropin was used to prevent adrenal atrophy, a normal boy was born. There were no congenital defects present two years after birth, and the infant required no steroid therapy. (The patient was treated in collaboration with Dr. David Graller and Dr. Leon Goldman, of Cincinnati.)

Physicians accustomed to thinking of systemic lupus erythematosus as a fulminating, invariably fatal disease may be skeptical of the diagnosis of systemic lupus erythematosus when the patient is not obviously ill. These studies reveal that this particular type of patient may be in grave danger. While not appearing sick, these patients still carry the crucial characteristics of lupus erythematosus, i. e., the capacity to exacerbate quickly and severely to the stress of relatively minor infections. Cases 4 and 5 are two such examples. It is in these subclinical atypical forms of systemic lupus erythematosus that the decision to use steroid therapy is debatable.

If both the patient and the attending physician can be made aware of the potentialities of the disease, it is better to withhold specific therapy until an acute exacerbation occurs. On the other hand, once steroid therapy is started in these patients, great caution must be exercised before the drugs are discontinued.

CONCLUSIONS

A survey is presented of 83 observed patients with positive plasma L. E. tests for systemic lupus erythematosus. A comparison between the steroid-treated and the nonsteroid-treated patients with similar degrees of illness reveals the following effects ascribable to steroid therapy: (1) a dramatic, often life-saving effect on the severe fulminating course of systemic lupus erythematosus which leads to (*a*) a lengthening of life through the use of continuous, uninterrupted maintenance therapy, (*b*) an improvement in morbidity; (2) a failure to improve certain patients, especially those with progressive renal disease.

ABSTRACT OF DISCUSSION

DR. FRANCIS E. SENEAR, Chicago: First, I want to congratulate Dr. Haserick on this splendid and very worthwhile presentation. I think that all of us are aware of the wide variety of conditions in which these agents have been used and where the evaluation with many of them has been incomplete, and with many of them we feel, particularly not in our hands but in those of others, the drugs are much too widely used.

I think Dr. Haserick has been very conservative in separating the types of subacute disseminated lupus erythematosus which are now included on the basis of the L. E. test and has excluded them from his figures so that the difference in fatalities, a reduction from 90% to about 30%, as he points out, lets us feel, on the basis of statistics in a large number of cases, that we certainly have an extremely valuable agent in the treatment of the disease, which always before, for all practical purposes, ended fatally.

I appreciate very much, as I think most of us will, the evidence which he has brought forward with regard to the comparative values of the different types of test for the lupus erythematosus cell and the pitfalls which we may encounter when they are not carried out by persons who are competent to do them and who are not acquainted with the possibilities of failure.

He has had the opportunity to study a very large number of cases. We have not been so fortunate. In a research and educational hospital, our experience has been relatively limited, because we have a small number of beds for the handling of patients in that institution. We have had eight cases within the past two years, and I have checked, after having the opportunity of seeing Dr. Haserick's original manuscript; our experiences with a small number of cases are, of course, parallel. We have had two deaths in our eight patients. Two of our patients were in the teen-age period, three in the 20's, and three in the 30's. One was a boy 15 years of age; the other seven were, as we would expect, girls. The boy was brought in in a moribund state, not quite in a crisis, but we would not have expected him to have lived more than two or three days, but he was brought through it very nicely. He went back to his home in southern Illinois and was continued on maintenance cortisone therapy and after several exacerbations finally died. We did not have the opportunity to have an autopsy performed in that instance.

The other death was that of a young woman 22 years of age who came into the hospital in a very severe state; an intractable diarrhea developed, possibly as a result of the chlortetracycline (Aureomycin) therapy, which was used as support. She finally recovered from that, and then a jaundice developed, and she died very quickly. At autopsy she was found to have had severe edema of the lungs, with hemorrhage, an enlargement of the liver with the jaundice, and probably the immediate cause of death, as Dr. Haserick has pointed out, or rather the ultimate cause, was a hemorrhagic nephritis. But with the other patients, we have had results comparable to Dr. Haserick's experience.

I think that several things in his manuscript which he did not have opportunity to bring out and which I had the opportunity to see are well worth repetition, and he may want to comment upon those in his closing discussion. They are, namely, the procedure to be adopted with those

patients who have the subacute type of involvement but who may at any time go into the very acute phase and the question as to whether or not it is wise to institute treatment with the steroids in this phase. I would like to have him give us his opinion about that in closing, because we have had one experience of that type where we saw a young woman in the office who eventually ended up in the hospital. She had a typical subacute type with minimal systemic involvement, and within a week after we saw her, although the disease had been present for several months, she suddenly went into the acute phase. She came out of it all right, and we have been able to keep her alive with maintenance therapy, although she has been back several times.

Dr. Haserick also did not have time to comment upon the importance of maintenance therapy after these people leave the hospital. I hope he will say something about that also in closing.

One other thing, he spoke of the one suicide and the three psychic episodes in our group. We find that the people in the Neurologic Institute have considerable difficulty in differentiating between those episodes which are caused by the steroid therapy and those which may be a part of lupus erythematosus. One of the patients had her psychotic episode before she came into the hospital, before she had the steroid therapy; the other two had them while under therapy. It is a very important decision to reach as to whether one has to discontinue the therapy because of the psychic episodes or whether the psychic episodes may be due to lupus erythematosus itself.

Dr. Frank C. Combes, New York: I certainly have enjoyed Dr. Haserick's review of the treatment of this distressing disease with the steroids. He has shown us what can be done with the conservative administration of steroids and the proper selection of cases.

I often have wondered whether one was justified in giving steroid therapy to any of these patients, even though they do respond to it. However, I think that in a disease such as this, which undergoes spontaneous remissions, one is justified in treating it during the acute exacerbations anyway, and we certainly are able to lengthen the patients' lives in relatively good health.

I think that we were the first ones to treat this disease with corticotropin at Bellevue Hospital. That was in the spring of 1949. It was before the demonstration of the lupus erythematosus cell, so we had no way to diagnose it along the lines suggested by Dr. Haserick. The cases were reported in the *Journal of Laboratory and Clinical Medicine* in December, 1949 (**72**:563-565). Unfortunately, the patients died.

We had sufficient material for only five days' therapy. One patient had a severe lupus erythematosus crisis with polyserositis and arthritis, was unable to take nourishment by mouth for several days, and had run a temperature of 102 to 104 F. for several weeks which did not respond to anything. We tried everything, including 1,000,000 units of penicillin daily. It was anticipated that any day she would die. Then, 150 mg. of corticotropin were given intramuscularly in six daily doses for five days. Well, you never saw such a dramatic improvement in a patient. Within 12 hours of the initiation of therapy, the temperature returned to normal; the arthralgia was relieved; the patient became euphoric and three days later was out of bed and eating heartily. The cutaneous lesions disappeared completely in about seven days. The total and relative eosinophilia disappeared; the leucocyte count increased from 6,000 to 11,000 per cubic millimeter; the lymphocytes dropped from 48% to 23%. However, the erythrocyte sedimentation rate was not changed. The urinary ketosteroids increased from 5.2 to 27 mg. Four days after stopping the administration of corticotropin, the patient went into sudden relapse and unfortunately died.

I wish again to thank and congratulate Dr. Haserick on an excellent presentation.

Dr. Jacob H. Swartz, Boston: I would like to ask Dr. Haserick about false positive lupus erythematosus cell reactions and whether it is minimized by the plasma dog cell technique. I have reference particularly to patients who have been given massive doses of penicillin.

Dr. Clinton W. Lane, St. Louis: I would like to inquire if Dr. Haserick has any hesitancy in prescribing cortisone (Cortone) acetate for pregnant women.

A woman aged 35 years was seen in the third month of pregnancy with a severe herpes gestationis. She had been observed through three previous pregnancies, in each of which herpes gestationis was extensive and severe. On two of these occasions the eruption persisted for several weeks after delivery. There was a rapid dramatic response to cortisone therapy, with complete disappearance of all lesions in one week. A maintenance dose of 100 mg. of cortisone acetate daily was necessary to prevent recurrences of the eruption. The patient was delivered of a three weeks premature dead fetus with several bony and cardiac malformations.

In a discussion of the case at the St. Louis Maternity Hospital several obstetricians were of the opinion that cortisone administered during the first half of pregnancy was more hazardous than when given during the final three or four months. Has Dr. Haserick had a similar experience, and does he agree with this opinion?

DR. RICHARD S. WEISS, St. Louis: I, too, very much appreciate Dr. Haserick's report, and I think it is going to be of great help to us in the future conduct of these cases.

I have had under observation two patients who were pregnant and who had subacute lupus erythematosus, but neither had gone into an acute crisis. The institution of cortisone therapy was begun early in the pregnancy, and they were carried through the pregnancy without any untoward events. They were delivered of normal children. At the termination of their pregnancy, no objective evidence of lupus erythematosus was present, and one of them three months after termination of pregnancy was objectively well but still had a positive L. E. test. The other one quite recently delivered and remains objectively and subjectively well. These two patients are on supportive cortisone therapy at the present time. They are two very fortunate women, and I am very much interested in hearing reports about others who have been treated while pregnant.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: I am sure we have all enjoyed Doctor Haserick's presentation and will read the extended manuscript with interest. It is difficult to make a statistical analysis of the effectiveness of treatment in a disease noted for its irregular and unpredictable course. With the practical application of the researches of Hargraves and Haserick during the past five years, the scope of systemic lupus erythematosus has been broadened to include many phases of the disease which are not classical, that is, patients with rheumatic syndromes, forms of purpura, cerebrovascular and convulsive disorders and states of weakness, fatigue and fever in young women with leucopenia, anemia, and disproportionate elevation of the sedimentation rate of the erythrocytes. In many of these the skin signs are transient, atypical, or absent altogether.

In the old days, patients who died with fulminating symptoms of acute disseminated lupus erythematosus were automatically classified in the acute stage of the disease, as in the 10 patients listed here. At the present time our classification is more elastic; those who show suggestive symptoms and manifest a positive Hargraves' phenomenon are classified as having systemic lupus erythematosus.

In following such patients over long periods of time and by carefully evaluating the history of previous illness, we are able to reconstruct a course of systemic lupus erythematosus which may involve ups and downs over a period of many years. It is well known that the course of the disease in men is unpredictable; by the same token, women who are in their 40's or approaching the menopause usually show a milder reaction than younger women. All these factors bear on the prognosis of a given case and influence the judgment in deciding the effectiveness of treatment.

Waiving all these considerations, it is still the clinical impression of competent observers that the course of the disease in its fulminating phases has been tempered by the use of cortisone and corticotropin. The patient has been tided over crises that would ordinarily have been disastrous, and life has been prolonged. One insurmountable handicap remains when damage has been done to the kidneys. In most instances this is irreparable.

This does not mean that, once the diagnosis of systemic lupus erythematosus has been made, in every case of this type the patient is a candidate for steroid therapy. More than ever, the management of the problem must be analyzed individually. Occasionally Hargraves and I have been confused by the interpretation of a weakly positive plasma reaction for lupus erythematosus. This has happened in patients with periarteritis nodosa, rheumatoid arthritis, and in two cases of dermatomyositis. Usually when there is a doubtful interpretation, one or more of the factors which go into the reading of the test are absent, namely, chemotaxis, nucleolysis, or phagocytosis, which produces the L. E. cell. The subsequent course of the patient and repeated examinations of the blood usually clear the issue.

In judging the prognosis and the therapeutic indications in patients with systemic lupus erythematosus, we must avoid the feeling that the demonstration of the L. E. cell itself consigns the patient to an inevitable end. Those who carry the worst prognosis are young women, especially redheads with fulminating symptoms and particularly with the irreversible burden of renal impairment. Such patients may be tided over one or more crises, but they rarely recover.

It may be well to emphasize a point in the management of persons who have been treated with cortisone or corticotropin and at some later date, perhaps a few months afterward, are faced with a situation involving stress, such as pneumonia or major surgical procedure. No one can judge the ability of the adrenals to return to normal after their function has been temporarily suppressed by such therapy. Fortunately, in most instances the return is normal, but instances are being reported where patients have died of adrenal insufficiency when faced with unusual stress. It is wise, therefore, in any patient who has had therapy with cortisone or corticotropin, even six months previously, to fortify a stress situation with the intramuscular injection of cortisone as a precautionary and a protective measure.

DR. EARL D. OSBORNE, Buffalo: I would like to ask Dr. Haserick to comment on two or three points of practical significance.

As was mentioned, I believe, at a meeting last year of hematologists, we have false positive tests from the effect of penicillin. I wish he would say something about that, because our hematologists are very much concerned with the false positive test from penicillin.

Furthermore, is there any relationship between the number of L. E. cells seen in the plasma test and the severity of the disease? It seems that too many dermatologists are going too much on the number of lupus erythematosus cells found in measuring the severity of the disease, rather than on clinical observation.

One more point, has Dr. Haserick seen any negative lupus erythematosus cell tests in systemic lupus erythematosus that have lasted for any significant time, and what experience has he had as to the significance of this negative phase when it has lasted for three, four, or five months?

One more practical point is the evaluation of corticotropin (Acthar Gel) in comparison to cortisone by mouth in maintenance doses. We have the impression that the corticotropin seems to be more effective than cortisone by mouth as a maintenance dose.

DR. JOHN R. HASERICK, Cleveland: I wish to express my appreciation to the discussers for their kindness.

Dr. Senear raised the question of what should be done about the subacute types of lupus erythematosus.

One would prefer not to treat a patient with steroid therapy, if he were not acutely ill and also if adequate facilities were not available to check the blood chemistry values.

With respect to the maintenance program, the second phase in the treatment of lupus erythematosus—the first phase being the hospitalization for the acute stage—requires small doses (10 units per day) of corticotropin along with the cortisone. We have found patients who like one type of corticotropin in preference to another type.

If corticotropin is used as the maintenance drug, as Dr. Osborne mentioned, booster doses of cortisone are used. For example, 50 mg. of cortisone acetate might be used on the day of an expected premenstrual flare-up. For an operative procedure, such as an appendectomy, 100 mg. of cortisone acetate is used on the day of the operation and 50 mg. the day after, and then the original corticotropin maintenance program is resumed. Booster doses, therefore, are important, and I think one should err on the side of giving too much, rather than too little.

In regard to the false positive lupus erythematosus tests, I had the privilege of reviewing Walsh and Zimmerman's positive lupus erythematosus test preparations in those patients who had penicillin reactions. They were unquestionably the L. E. phenomenon in my opinion. However, they were a very low-grade positive.

We have seen similar false positive reactions in the hydralazine hydrochloride (Apresoline)-treated hypertensive patients, who have had arthritis and polyserositis along with these very weak positive lupus erythematosus tests. The relationship between the number of cells or the degree of positivity and severity, I think, is rather an important one. In our experience we have never seen a false positive lupus erythematosus test in the 3+ or 4+ group. It is only in the lower grades of the L. E. tests that these difficulties arise.

We have seen a number of patients enter into periods during which the L. E. test turned negative. This is evidence that the patient is doing well. The single exception is in the patients who have uremia. As they enter the final uremic phase, in our experience, the L. E. test is very often seen to turn from positive to negative, so that one might be misled into feeling that the patient is doing well, when actually, of course, the final phase is near.

Clinical Notes, New Instruments and Techniques

MECHANICAL ADJUVANT FOR DERMATOLOGICAL BATHS

LIEUTENANT COLONEL WILLIAM N. PIPER
AND
LIEUTENANT COLONEL JOHN F. KUITERT
MEDICAL CORPS, UNITED STATES ARMY

Recently a portable apparatus, the Vibra-Bath [1] has been developed which has proved a dependable therapeutic adjuvant for dermatology. This apparatus makes possible any combination of medicated or cleansing baths with gentle mechanical cleansing, effleurage, and percussion and compression massage, with or without heat, in an easily available manner through the utilization of closely packed air bubbles delivered through varying water depths. The physiological principles and mechanical benefits of hydromassage have been understood and utilized in physical therapy clinics for many years. The application of hydromassage in the management of certain dermatological conditions has been limited only by the availability of this means of treatment to the dermatologists.

The unit, operating on normal house current and weighing less than 19 lb. (8.6 kg.), consists of a power unit, air-flow tube, and a Vibra plate. A control panel, located on the power unit, consists of three switches—power, heat, and air volume. The heat switch permits the heating of the column of air to a maximum of 170 F. The air-volume switch permits selection of three motor speeds—low, medium, and high—and thus controls the column of air delivered to the water through the Vibra plate, which is attached to the bottom of the tub by suction cups. The maximum capacity delivered is approximately 50 cu. ft. (1.42 cu. m.) per minute, developing an intense rate of ebullition. This dense mass of air bubbles, rising through a column of water, creates a succession of varying pressures upon the skin and underlying tissues, the degree of stimulation depending upon the size of the bubble, its velocity, and the surface tension of its wall. These relative pressures may be analyzed as (*a*) a positive pressure at the moment the bubble wall impinges upon the skin, (*b*) a pulsating pressure during the interval that the bubble adheres to the skin and is compressed by the column of water, and (*c*) a negative pressure as the bubble disengages itself and rises to the surface of the water column. At low speed this single action described is multiplied by the thousands of bubbles which impinge upon all the skin area in contact with the air-water column. As the water depth is increased or as the power is increased to medium or high speed, the bubbles decrease in quantity but increase in size and speed, impinging upon the skin in the form of a churning, pushing water mass. By varying the size of the air bubble and the intensity of the ebullience, a complete range of action may be obtained.

Massage may be divided into three major classes: compression, percussion, and stroking, and into two minor classes—stroking and vibration. Stroking is further classified into effleurage, superficial stroking, and deep stroking. The effect of compression and percussion on the skin and underlying tissue is vasodilatation.

The following are recommended dermatological indications: (1) effleurage, the gentle stroking and vibration secured through the use of the low speed, indicated for routine medicated

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This report does not constitute endorsement by the Department of Defense for the product Vibra-Bath.

From the Walter Reed Army Medical Center, Walter Reed Army Hospital, the Dermatology and Syphilology Section, Lieut. Col. William N. Piper, Chief, and the Physical Medicine Service, Lieut. Col. John F. Kuitert, Chief.

1. Manufactured by Birtcher Corporation, Los Angeles 32; approved by Underwriters Laboratory E—16801; submitted for approval to the Council of Physical Medicine and Rehabilitation, American Medical Association.

and cleansing baths; (2) superficial stroking, secured through the use of the medium speed, indicated for removal of heavy scales and adherent crusts without the production of vasodilatation; (3) compression and percussion, secured through the use of the high speed, where vasodilatation and erythema are desired, in addition to the other actions listed above. Heat

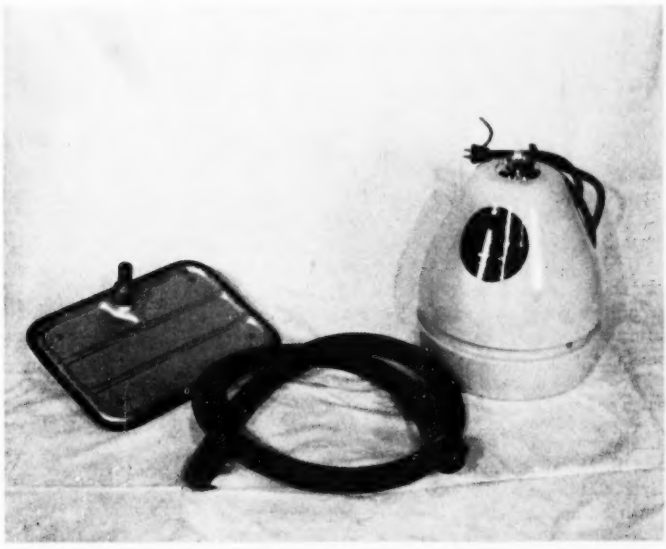

Fig. 1.—Apparatus disassembled.

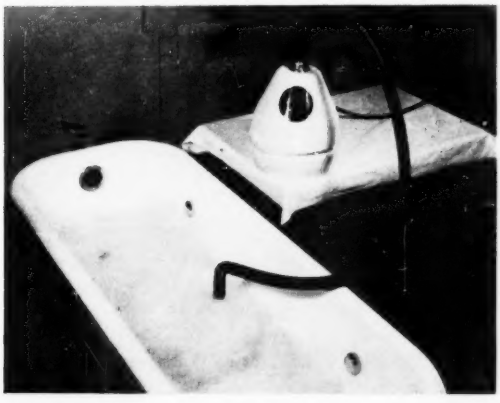

Fig. 2.—Apparatus in operation at "low" motor speed.

therapy, if indicated, is available through heated bath water, the temperature of which may be maintained by the heating unit.

Contraindications include debilitating diseases, fever, and phlebitis. Patients with skin diseases in which vasodilatation is contraindicated should not be exposed to compression and percussion massage as secured by the high motor speed.

The advantages of this apparatus are that it is relatively inexpensive, may be safely used in the home or dermatology wards, increases effectiveness of the bath, requires a shorter time

period, will not be injured or plugged by medications, provides for a continuous bathing of the skin, aids in the removal of scales and crusts without trauma, and efficaciously combines the best features of controlled bath and hydrotherapy.

Patients' acceptance of this form of therapy has been unusually high. In addition, it provides a psychological effect which is audible, tactile, and visual, and which cannot be overlooked as a beneficial contributory factor in the problem of day-to-day patient care.

PARAAMINOBENZOIC ACID AS A SUNSCREEN

ALEXANDER A. FISHER, M.D.
WOODSIDE, L. I.

Kesten and Slatkin [1] confirm the work of Rothman and Rubin [2] on the excellence of paraaminobenboic acid as a sunscreen. Rothman, in discussing this paper, comments on the difficulty of making smooth creams with the free acid.

For some time, I have been using the following cream, which is a smooth elegant preparation of 15% paraaminobenzoic acid. It consists of 4.5 cc. of paraaminobenzoic acid, 6.0 cc. of distilled water, 6.0 cc. of hydrophilic ointment, and add vanishing cream to make 30.0 cc.

The pharmaceutical instructions are as follows: Levigate the paraaminobenzoic acid with water to a smooth paste. Add hydrophilic ointment, and finally add the required amount of vanishing cream. The vanishing cream used may be that of any reputable cosmetic firm.

As Rothman points out, this preparation is an excellent sunscreen and it is much less sensitizing than the esters of paraaminobenzoic acid.

1. Kesten, B. M., and Slatkin, M.: Diseases Related to Light Sensitivity, A. M. A. Arch. Dermat. & Syph. **67**:284, 1953.

2. Rothman S., and Rubin, J.: Sunburn and Para-Aminobenzoic Acid, J. Invest. Dermat. **5**:445, 1942.

TARSONEMUS CONFUSUS

Contaminant of Fungus Cultures

FREDERICK REISS, M.D.
AND
LEONA CAROLINE, A.B.
NEW YORK

Specimens of fungous cultures kept in refrigerators can be preserved for a considerable length of time without risking contamination. However, culture collections which are not stored in refrigerators but are exposed to the dust in cabinets are at times attracted by mites.

After perusal of the available American literature we found that no mention is made of these contaminants, and therefore we deem it of interest to report our findings.

PRESENT FINDINGS AND REVIEW OF LITERATURE

On examining a culture mount of a month-old Microsporum lanosum culture we observed a typical mite with several ova (Figs. 1 and 2), which was identified as Tarsonemus confusus Ewing. There was no macroscopic evidence on the surface of the culture which would have indicated such an infestation.

The only informative reference which we have traced is that of Langeron,[1] who considers these mites as "the enemies of fungus cultures." The mites belong to two genera, Tarsonemus and Rhizobium.

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School (Dr. Marion B. Sulzberger, Chairman) and the Service of Dermatology and Syphilology of Bellevue Hospital (Dr. Frank C. Combes, Chief of Service).

Acknowledgment for the identification of the mite is made to Dr. Edward Baker, Agricultural Research Administration, Division of Insect Detection and Identification, Washington, D. C.

1. Langeron, M.: Précis de Mycologie, Paris, Masson & Cie, 1945, p. 506.

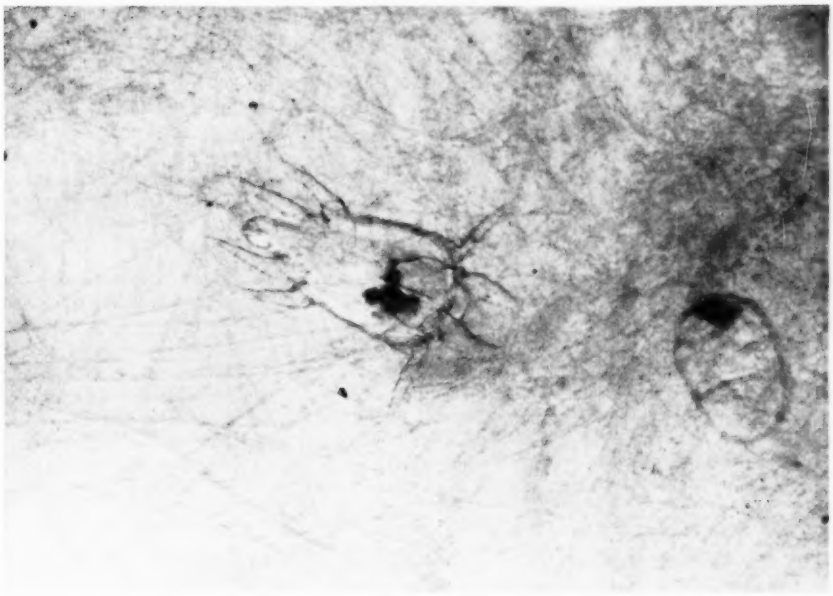

Fig. 1.—Tarsonemus confusus Ewing and ovum amid a mycelium of M. lanosum.

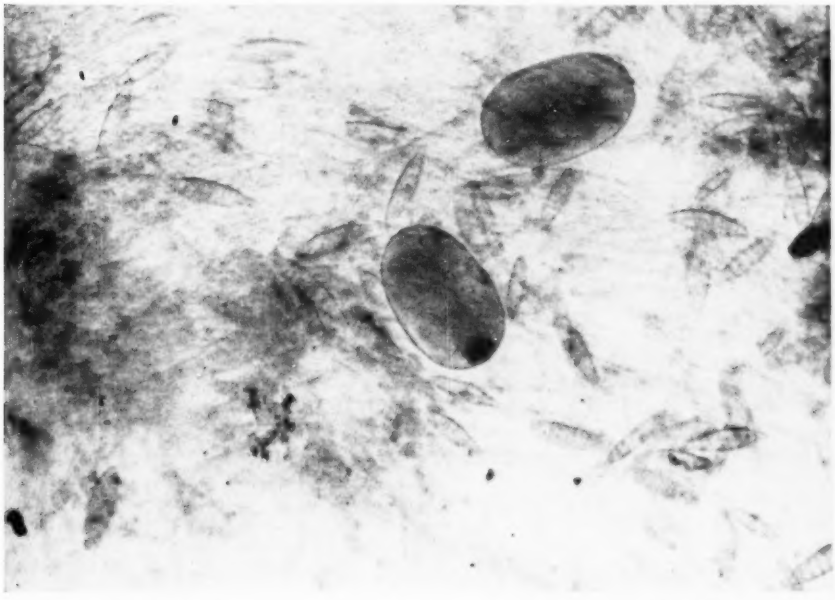

Fig. 2.—Ova of Tarsonemus confusus amid several macroconidia of M. lanosum.

These mites thrive on dust and are attracted chiefly by the musty odor of nocardias and yeasts. According to Langeron these mites are not satisfied to invade or destroy one culture, but migrate from tube to tube.

This migration may cause the destruction of an entire collection within a rather short period. The only visible macroscopic sign of such an infestation is described as a *moiré*-like design caused by the overgrowth of certain bacteria which are carried by the mites into the culture tubes. These bacterial colonies are easily recognizable with a loop as tiny whitish or grayish specks. At times not only bacteria are carried with these mites but other fungus contaminants, such as Actinomyces albus, Acremonium, Eurotium, Cephalosporium, and Fusarium.

PRECAUTIONS AGAINST AND DESTRUCTION OF THE MITES

Beside meticulous cleanliness of the cabinets and incubators, the cotton plugs of culture tubes should be inserted tightly. Puntoni [2] recommends that the cotton plugs be dipped into petroleum and stoppered tightly after drying. Duche [3] advises that cultures be kept in large glass cylinders the bottom of which should be covered with gauze in order to prevent breakage of culture tubes. All this material must be sterilized by dry heat. A small amount of glue should be applied around the inner circumference of the cylinder midway between the opening and the bottom. This may prevent the passage of the mites into either the culture tubes or to the adjacent cylinders.

None of the above-mentioned precautions are, however, an absolute guarantee against a possible infestation with mites. Infestation occurs particularly when cultures have a smell attractive to mites and are stored in a warm room or in incubators, which enhances the hatching of the ova.

SUMMARY

A mite, identified as Tarsonemus confusus Ewing, infesting a M. lanosum culture is reported. Appropriate prophylactic measures are described.

870 Fifth Ave. (Dr. Reiss).

2. Puntoni, V.: Infestation des cultures de champignons par des acariens du genre Tarsonémus: Préservation de ces cultures, Ann. parasitol. **9**:359, 1931.

3. Duche, J.: Technique mycologique: Entretien des mycotèques, Compt. rend. Soc. biol. **112**:124, 1933.

SUBSTITUTE FOR LIQUID NITROGEN

EDWARD J. RINGROSE, M.D.
BERKELEY, CALIF.

Liquid nitrogen cryotherapy is an almost indispensable modality for those who have learned its virtues. However, it may not be available at any time for some and not always available for others.

An effective substitute is carbon dioxide slush. Though slower in producing freezing than liquid nitrogen, it is more rapid, more adaptable to irregular lesions, and freezes more uniformly than solid carbon dioxide. It may be quickly prepared as follows: Carbon dioxide snow, collected in the usual chamois-skin bag, is placed in a half-pint Thermos bottle (preferably of the squat, wide-mouth type, for ease in dipping with an applicator) and acetone added with stirring until a slush of the desired consistency (not too wet) is obtained. This is then applied to the appropriate lesion—seborrheic keratosis, verruca, senile keratosis, molluscum contagiosum, etc.—with a cotton-tipped applicator until a white halo develops about the lesion.

If multiple lesions are being treated it may be desirable to use a fresh applicator during the procedure in order to absorb any excess acetone and prevent running of the slush onto normal skin.

As with liquid nitrogen, one treatment is usually all that is necessary, though occasionally repeated treatments at intervals of about three weeks may be required.

Carbon dioxide slush kept in a Thermos bottle capped with a small vented cork will keep for several hours.

Society Transactions

CINCINNATI DERMATOLOGICAL SOCIETY

Alfred Weiner, M.D., President

Raymond Suskind, M.D., Secretary

January 7, 1953

Tabetic Crisis, Treated with Intravenous Corticotropin (ACTH). Presented by DR. A. L. WEINER.

The patient first came under observation in December, 1947, at which time there was an episode of severe and persistent abdominal distress with marked nausea and vomiting. At that time the serologic test for syphilis was positive, and the spinal fluid showed positive serologic reaction and contained increased amounts of protein and increased numbers of cells. The physical and neurological findings were indicative of tabes, and the diagnosis of tabetic crisis was made when other possible causes for the abdominal symptoms were excluded (including x-rays). This attack failed to respond to anodynes and other forms of therapy and to antisyphilitic treatment but disappeared spontaneously after a period of some two weeks. Following dismissal from the hospital, treatment consisting of 10,000,000 units of penicillin, followed by one year of chemotherapy, was given, and the patient was lost from observation.

There was no further difficulty until Dec. 9, 1952, when the patient became acutely ill with severe nausea, vomiting, and retching, accompanied with low-grade fever. The abdomen was soft, and there were no masses. There was no pain. The vomiting continued unabated for several days, and the patient was admitted to Mercy Hospital on Dec. 15, 1952, where no apparent cause for the persistent vomiting and abdominal distress could be determined. The blood cell count was normal, as was the urine. The patient was treated by means of intravenous fluids, antibiotics, anodynes, and large doses of various types of vitamins. An atonic bladder developed, and it was necessary to catheterize the patient.

The patient was seen in consultation on Dec. 16, at which time persistent nausea, retching, and vomiting had been occurring for the preceding seven days. There was considerable dehydration and weight loss. The result of neurologic examination was indicative of tabes, with fixed unequal pupils and hyperreflexia. Intravenous injections of dextrose had been given, without relief.

Ten milligrams of corticotropin (ACTH) in dextrose in saline was given by intravenous drip, and the patient stated that within 30 to 45 minutes the vomiting had lessened and that within the next several hours it had almost ceased. Fifteen milligrams of corticotropin was given on the following day, and this dosage was repeated four times daily. The patient arose from her bed and was able to void. All vomiting, retching, and nausea had completely disappeared in 36 hours.

The serologic tests for syphilis were positive, and the spinal fluid was normal, with reference to cell count, protein, and serologic reaction during this hospitalization. The patient was dismissed from the hospital on Dec. 23, 1952, and there has been no recurrence of the symptoms.

DISCUSSION

DR. ROY KILE: This is an interesting report and to my knowledge the first one of the use of corticotropin for this very disturbing reaction. The prior control use of pure dextrose drip shows the value of the additional drips with the corticotropin added.

Lichen Sclerosus et Atrophicus in a Linear Scleroderma. Presented by DR. ROY KILE.

S. A., age 40, had an eruption after a burn nine years ago. Her right arm became weak, and she lost use of it for six months, eight years ago. She was observed first in 1941. She was presented to the Cincinnati Dermatological Society in 1942, and all agreed on a diagnosis of

linear scleroderma of both arms and shoulders. Photographs and a specimen for biopsy were taken at that time. She was not seen for six years. During that time the lesions softened and became pigmented under no treatment. Strength returned in the right arm. In 1948 she presented white patches in areas over the right shoulder, with follicular plugging and atrophy. These developed in areas of scleroderma. She has had chronic otitis media for many years. Two biopsies were made. Lichen sclerosus et atrophicus was confirmed in the section by Dr. Hamilton Montgomery.

She has had no therapy. The lesions have faded somewhat.

Nevus Syringoadenomatosus Papilliferus of the Scalp. Presented by DR. D. J. KINDEL and DR. FORMAN FRIEND.

F. B., a white woman, age 36, had a scalp lesion near the vertex. This had been present since birth but in the last few years had bled and discharged serous material. The lesion was oval, about 1¼ by 1 in. (3.18 by 2.54 cm.), and was elevated about ¾ in. (1.91 cm.). The surface was granulomatous in nature, salmon pink in color, and oozed serous material. The biopsy revealed a typical nevus syringoadenomatosus papilliferus.

Surgical excision removed the lesion entirely.

DISCUSSION

DR. JOHN SQUIRES: The clinical appearance of the lesion suggested a granuloma pyogenicum.

DR. ELMER LOOMIS: The last case of this type presented to the Society was one of the vulvar area, where there was some difference of opinion regarding the differential diagnosis between this disorder and a metastatic adenocarcinoma of the cervix. Can pilocarpine injections be used as a diagnostic aid?

DR. D. J. KINDEL: Lesions of nevus syringoadenomatosus papilliferus have been observed on the scalp, as well as in the perineal areas. Pilocarpine can be used to observe sweat droplets on such a lesion.

Marfan's Syndrome—Panniculitis, Arthrogryposis, and Arachnodactyly. Presented by the DEPARTMENT OF DERMATOLOGY AND SYPHILOLOGY, CINCINNATI GENERAL HOSPITAL.

T. L., a Negro girl, aged 18 months, presents a peculiar hide-bound skin with subcutaneous induration and failure to gain weight and develop normally.

This child, born of a nine months' uncomplicated pregnancy, weighed 4 lb. 7½ oz. 2,005 gm. and showed arachnodactyly at birth. The parents and four other children are all normal. The child was hospitalized at 5, 7, and 10 months of age because of failure to gain weight, underdevelopment, bronchopneumonia, and diarrhea. On first examination by the staff of the Department of Dermatology, a peculiar hide-bound skin with subcutaneous induration was noted. A biopsy of a specimen of the skin was read as panniculitis of undetermined etiology. X-rays of long bones showed gross retardation of bony maturation, and the skull showed "osteogenesis imperfecta." Results of an orthopedic consultation indicated a diagnosis of arthrogryposis, and it was suggested that the flexed lower extremities should be placed in a cast to correct the flexural contractures. Results of a neurologic consultation disclosed no hydrocephalus or other neurological abnormalities. Findings of an eye consultation revealed no ocular abnormalities. Pyelogram findings following intravenous injection of contrast medium were normal. Electrocardiogram findings showed dextrocardia. Clinically the child showed both physical and mental underdevelopment.

A blood cell count showed 3,280,000 red blood cells and 8,100 white blood cells, with 49% lymphocytes, 47% polymorphonuclear leucocytes, 1% monocytes, 1% basophiles, and 2% eosinophiles. Serologic reactions for syphilis were negative (Kahn).

Other laboratory findings were as follows: serum calcium 9.0 to 12.5 mg. per 100 cc., phosphorus 3.5 to 6.2 mg. per 100 cc., phosphatase 6.1 to 7.8 Bodansky units, total protein 5.3 to 5.8 gm., albumin 3.3 gm. per 100 cc., globulin 2.0 gm. per 100 cc., albumin-globulin ratio 1.7, nonprotein nitrogen 67 mg. per 100 cc., chlorides 570 gm. per 100 cc., and cerebrospinal fluid normal.

Mycosis Fungoides—Investigative Studies with Local Injection of 17-Hydroxycorticosterone (Compound F) and the Topical Application of Radioisotope Sr^{90}. Presented by the DEPARTMENT OF DERMATOLOGY AND SYPHILOLOGY, CINCINNATI GENERAL HOSPITAL.

K. S., a 30-year-old white woman, presents a tumor phase of mycosis fungoides, confirmed by biopsy performed as early as 1948.

In 1943 a small area of dermatitis developed on the left hip. In 1948 a few more infiltrated lesions had developed. In 1949 (January) the patient was hospitalized and treated with nitrogen mustard. Subsequently she received five courses, one in 1950, two in 1951 (February and October), and two in 1952 (February and August). On two other occasions she also was given nitrogen mustard orally. She received P^{32} without benefit.

In March, 1950, the patient was started on cortisone acetate and took 50 to 75 mg. daily until August, 1952. The steroid aided the pruritus and the erythematosquamous and "eczematous" phases but not the tumor phases. The drug also reduced the side-effects of nitrogen mustard. From March until July, 1952, the patient received corticotropin (ACTH) weekly by intravenous drip. In August, 1952, during her last course of nitrogen mustard, there was an extravasation of nitrogen mustard into the subcutaneous tissue of the dorsum of the right hand. A suppurative cellulitis developed, which necessitated incision and drainage on Sept. 19, 1952. Staphylococcus aureus was cultured out.

The last course of nitrogen mustard resulted in only a slight remission of the lesions. With discontinuance of the drug, the eruption became increasingly worse. An erythematous scaly patchy dermatitis developed and then became generalized. Some of these areas were exposed to the application of Sr^{90} for variable intervals, and some lesions showed partial to complete regression. Those which were deeply infiltrated did not respond as well as those which were superficially infiltrated. In addition, the patient had repeated injections of cortisone and various types of 17-hydroxycorticosterone (Compound F) by syringe, by needle, and by Hypospray jet injection apparatus to determine the local effect of the steroids. A definite decrease in the nodules was produced in each instance where 17-hydroxycosticosterone was employed. These were all controlled by detailed biopsy studies.

DISCUSSION

DR. SAENGER (by invitation): I will tell briefly of our experience in treating several small localized areas with Sr^{90} and about the physics of beta-ray applicators. The radiation therapist is becoming interested in the evaluation of beta radiation as applied to the lesions of the skin and the eye. Radioactive strontium is of particular interest, since it has a long life of 20 years, decaying to Y^{90}, which has a 65-hour half-life. The yttrium decays to stable Zr^{90}, giving off a beta particle of maximum energy of 2.16 mev. It is this beta particle which is used therapeutically. The effect of these beta particles is very superficial, and their absorption can be compared with various types of x-irradiation as Sr^{90}, 50% absorption at 1 mm.; 44 kv., 50% absorption at 4 mm.; 100 kv., 50% absorption at 1.2 cm.; 200 kv., 72% absorption at 2.5 cm.

The usual half-strength dermatological plaque containing 5 mg. of radium in an area of 1 sq. cm. will give about 7,000 rep in about one and one-half hours. A typical strontium applicator containing 25 mc. gives 31.1 rep per second. The effective treatment area is a circle of 4 mm. diameter. This applicator is fragile and must not be broken, since strontium is a bone seeker.

I think the interesting thing in this patient with mycosis fungoides was the excellent response in the very thin lesions with doses of 300 rep, 600 rep, or 1,200 rep. There was no evidence of recurrence in these areas within six to eight weeks after irradiation. I do not believe the thick lesions can be treated with this type of applicator. Other beta emitters are being investigated. Radioactive ruthenium and rhodium plaques give off beta rays of 3.55 mev maximum energy.

From a practical point of view this type of therapy is of value at present for very small and superficial lesions, especially when they are in rather inaccessible or moving parts of the body. It is a useful addition to our radiation armamentarium and as effective as radium.

DR. LEON GOLDMAN: Over a period of years this patient has provided us with the varying picture of exacerbations and remissions characteristic of mycosis fungoides. She has always had

a good response to intravenous injection of nitrogen mustard, without serious hematopoietic effects. She has not had good responses to oral nitrogen mustard. The infiltration of the tissues by the nitrogen mustard was a serious reaction almost necessitating amputation of her hand. Her poor veins have always been a hindrance for this particular therapy. Concomitant corticotropin or corticosteroid therapy has reduced somewhat the severe gastrointestinal reactions which she obtains from such therapy, the last two courses in massive doses of 0.3 mg. per kilogram of body weight. Dr. Kindel has been studying a type of weekly ambulatory nitrogen mustard therapy. Irradiation still offers the only effective and practical therapy for the recurrent tumor phase. Additional studies of various topical radioisotopes will be continued.

The patient to date has had some 52 local injection experiments with 17-hydroxycorticosterone, hydrocortisone acetate, in various vehicles and of various forms of 17-hydroxycorticosterone. The local injection of the acetate of 17-hydroxycorticosterone is the most effective, with definite local diminution of a significant portion of the inflammatory infiltrate. The detailed cytological changes of the tumor phase under local 17-hydroxycorticosterone therapy are under detailed study.

Exfoliative Dermatitis Complicated by Fatal Acute Disseminated Histoplasmosis.
Presented by DR. HARRY FOX.

A 17-year-old white girl, previously in good health, noted an eruption of the trunk in January, 1952, following an emotional episode. She was treated, evidently, as having a neurodermatitis and subsequently as having an allergic eczema by various physicians.

At first examination in October, 1952, she presented an eczematoid neurodermatitis-like eruption of the trunk and an id eruption at scattered areas generally. She was hospitalized on Oct. 6, 1952, and despite local measures the lesions spread, and she had a temperature of 101 F. one week later. Treatment with 100 mg. of cortisone (Cortone) acetate daily was begun, and the temperature and skin became normal within three days. She was discharged from the hospital, but treatment with cortisone was continued for a while. In the hospital she had no complaints, except that of itching and chilliness. The serology was negative; results of urinalysis and hemograms were normal. One week later the white blood cell count was 12,400, with 70% neutrophiles, 13% lymphocytes, 3% monocytes, and 14% eosinophiles. The serum sodium, potassium, and the plasma chlorides were in normal range repeatedly. The patient was given prophenpyridamine (Trimeton), promethazine (Phenergan), calcium gluconate, Bellergal (a proprietary composed of belladonna alkaloids, ergotamine tartrate, and phenobarbital), methylparafynol (Dormison), and other sedation and local therapy of wet dressings, lotions, pastes, and various baths, all without aid until the addition of cortisone. No antibiotics were given during this hospitalization period.

She was readmitted to the hospital 10 days later, having had no cortisone for six days. A generalized exfoliative dermatitis rapidly developed. Her temperature was 101 F., and the history indicated that the patient was well until two days previously. Her temperature was 103 F., when chlortetracycline (Aureomycin) was administered, and later oxytetracycline (Terramycin) was administered (250 mg. four times a day) without effect and after six days corticotropin (ACTH) was administered (80 mg. daily intramuscularly). The temperature and the skin were almost normal in 36 hours. One week later the temperature rose again (with 20 mg. of corticotropin twice a day), and administration of corticotropin was started via intravenous drip (15 mg. in 10 hours), along with penicillin and streptomycin.

The temperature remained elevated. The spleen and liver became enlarged, and adenopathy was present. Administration of corticotropin was discontinued after three days. Sudden clinical change for the worse was noted the next day, with severe abdominal pain and some pleural fluid from which Histoplasma organisms were recovered. Subsequently the blood likewise showed the organisms via both venous and capillary blood. The chest plate now showed a suspected miliary process. Adenopathy and hepatomegaly became rapidly prominent, and, despite transfusions and one dose of 2-hydroxystilbamidine (225 mg. intravenously), the patient died two days later.

The skin was clear at the time of death, except for petechial and purpuric lesions in small numbers at the chest.

Laboratory findings during this hospital stay included repeated urinalysis, with occasional sugar 1 to 2+ and albumin up to 100 mg. Repeated blood cell counts showed progressive

anemia and leucopenia in range of 5,000 to 6,000 white blood cells; platelets diminished to 35,000. Total proteins stayed around 4.6 gm. Blood sugar was 81 mg. Urea nitrogen was 8 to 20 gm. Total globulin was 0.15 gm.; electrolytes, including serum potassium and sodium and plasma chlorides, were in normal range. L.E. smear was negative. Stool examination was negative. Bilirubin was 5 to 1.0 mg. per 100 cc. Result of heterophile examination was in normal range; Salmonella typhosa, S. paratyphi, and Brucella abortus were negative. Electrocardiogram findings were considered abnormal, with nonspecific pattern.

Autopsy was obtained.

DISCUSSION

DR. GOLDMAN: I saw this patient once with Dr. Fox. She had an acute exfoliative dermatitis, with edema and areas of superficial bullous impetigo and areas of Bockhart. Dr. Fox's impression was that this was the result of a generalized spread of a toxic dermatitis. One would suspect contact dermatitis from the history.

My responsibility was to say whether it was safe to recommend continued corticotropin or corticosteroid therapy in the face of a skin infection which in this patient complicated an exfoliative dermatitis with hyperpyrexia. I felt that the patient was very ill from exfoliative dermatitis and was going to die because it was becoming progressive and that the antibiotic therapy was only feeble support. Since corticotropin therapy had been given before, with improvement of her skin, I thought that it could be repeated. I thought the fever could also come from exfoliative dermatitis. One can only speculate about the significance of the corticotropin and the corticosteroids and also the antibiotics on the activation of an intercurrent (active?) infection.

DR. KILE: Do you think corticotropin made her worse?

DR. GOLDMAN: My impression was that corticotropin helped her skin tremendously.

DR. FOX: As the history indicates, the patient was a young lady free of any kind of illness until the beginning of this year. The most disturbing part of her picture was the dramatic response of a desperately ill girl to the steroid therapy, with the disappearance of all skin manifestations and fever and then the abrupt onset of fever to 105 F. There were no longer any skin lesions to account for fever. It was at this time that the medical men were called in, and for the first few days there were no findings. Meanwhile, steroid therapy was abandoned, and pain developed on the right side of the upper abdomen and right chest, and after two days of such pain some pleural fluid developed. The pleural fluid was aspirated, and from that the diagnosis was made.

DR. HAMBURGER (by invitation): I saw this patient with Dr. Felson and Dr. Fox six hours before she died. The problem was why did she have pain in the abdomen? It seemed apparent that something had happened as a result of corticotropin therapy, possibly a ruptured viscus—we couldn't be sure—or possibly some generalized infection.

Physical signs were striking. There was a great deal of tenderness in the right upper quadrant, and the liver was enlarged. I thought she probably had liver abscess, a subphrenic abscess quite possibly associated with a ruptured viscus, or perhaps a ruptured duodenal ulcer. The possibility of generalized histoplasmosis didn't enter my mind. Pleural fluid, which was present the next morning, developed and I thought that it was a sympathetic reaction to what was going on beneath the diaphragm. Her pleural cavity was tapped, and Dr. Schwarz identified Histoplasma in the fluid. The patient lived just 24 hours after that.

How this came about is a matter of speculation. There are two possibilities: (1) that there was a focus of Histoplasma in the body some place and that under the influence of steroids the Histoplasma got loose in the blood stream and produced a fulminating infection; or (2) that she developed histoplasmosis while receiving corticotropin, and its effects were masked. The second possibility is highly unlikely, and the first is probably not likely in view of the circumstances under which this occurred. I don't know from a clinical standpoint how it could be proved. The whole mechanism of spread of infection under the influence of steroid hormones is a subject about which we know little. Steroids inhibit migration of leucocytes to a focus of infection, and that is the explanation offered for the experimental work in which hemolytic streptococci can overwhelm rabbits that are pretreated with cortisone, although there is little effect on the normal rabbit. There have been similar experiments with Brucella in guinea pigs and mice and similar experiments with tuberculosis. These are all experiments in which bacteria have been inoculated

in the animal. In no sense—and it is certainly true with streptomycin-treated animals with tuberculosis and animals with hemolytic streptococci and treated with penicillin—can the animal be saved with antibiotic therapy, despite the influence of cortisone or corticotropin. How a lesion which is present in the body, which has been quiescent and walled off to some extent, becomes opened up under the influence of steroids has not been explained. There is no evidence that these hormones promote the growth of bacteria or viruses or fungi in vitro. They are not growth-stimulating chemicals when added to culture media, and yet under their influence we know that in the experimental animal and in human beings these devastating things do occur.

In this girl's case, it should be pointed out that Dr. Fox had no choice. If the patient wasn't to die, something must be done. That carries with it theoretical risks. The patient did die, but, had she not been given corticotropin, she would have died of exfoliative dermatitis.

DR. WEINER: Have you known any other clinical situations where any type of infection, bacterial or otherwise, overwhelmed the patient treated with steroids?

DR. HAMBURGER (by invitation): A number of such situations have been observed. Lung abscesses have occurred. There have been two such cases in patients receiving steroids for rheumatoid arthritis. One patient was an otherwise intelligent man, who took treatment in his own hands and regulated his dosage. There have been cases of pneumococcal pneumonia deliberately treated with corticotropin, and in those cases bacteremia persisted, even though fever and other signs of clinical toxicity were held in abeyance by corticotropin. There have also been cases of tuberculosis; in these cases the patient has had tuberculosis in the past, and there were no healed lesions. There may be cases I haven't seen where tuberculosis has occurred with corticotropin and without previous lesions.

DR. WEINER: It seems probable that these substances may exert an influence upon the immunology of the patient. Currently, together with Drs. Rein and Loveman, we are participating in a study to determine the effects of cortisone and 17-hydroxycorticosterone (Compound F) on the serologic titer in syphilis. There have been previous reports concerning the effects of steroids on animals experimentally inoculated with syphilis. The first patient we studied locally was a woman with latent congenital syphilis and an unusually high serologic titer (40,000 dilutions). After only one week of intensive cortisone therapy and without any type of antisyphilitic therapy, the titer has become greatly reduced (1,800 dilutions). While the formation of reagin is not in any sense a measure of immunity in syphilis, still there is some tie-up with the immune phenomenon in a very broad sense. Of course, this is an isolated example, and I understand that such a reaction has not been the general experience thus far in these studies, but I think that it is of some interest in the discussion of the case under consideration.

DR. OLIVER: Even without thinking of histoplasmosis, in a case of exfoliative dermatitis of unknown origin we would be justified in examining the sternal marrow for evidence of a lymphoblastoma. If this had been done, it is quite possible that organisms would have been seen.

DR. GOLDBERG: In all disseminated cases are bone marrow examinations 100% positive for Histoplasma?

DR. FOX: There has been one patient in the literature that had exfoliative dermatitis in which histoplasmosis was demonstrated. This patient was a 43-year-old man who had a rash starting at the posterolateral areas and disseminating in a dry thick red process for about 16 years. A year and one-half before he died, Histoplasma organisms were found in the skin. I don't know whether they were found by culture, scrapings, or biopsy. In our case I understand that the biopsy at the time of death showed organisms. I am dubious that a biopsy done in January or at the time of dissemination would have showed organisms.

DR. JAN SCHWARZ: At autopsy we found disseminated histoplasmosis, with an enlarged spleen and liver, consolidation of all lung lobes, pleurisy, pericarditis, and general lymphadenopathy. There were isolated lesions in the kidneys but no gastrointestinal lesions whatsoever. We didn't feel that we should open the head, but we did a spinal fluid examination, which gave negative results microscopically and chemically; there was no increased protein. We can be reasonably sure that the brain and gastrointestinal tract were not involved. Diagnosis of the disease referred to is certainly most difficult clinically and anatomically. Anatomically we have seen cases which are proved by culture, and we are unable to demonstrate the organism in the tissues. At one recent meeting, 100 pathologists must have seen slides of a case of histoplasmosis,

and only 4 made the correct diagnosis. It is not easy, and nobody can be criticized for not finding it. Culture is still the best and simplest way to demonstrate it. The skin test is not too valuable; a positive skin test in an endemic area, with the population reaction close to 100%, does not mean much. If we have a positive test and suspect histoplasmosis, we should have a complement fixation which is reliable to find out if the lesion is active. Progressive histoplasmosis has increased titers in complement fixation, and one can be guided by this quite considerably. Last, the culture is simple to do from blood, bone marrow, sputum, bronchial washings, and even from the stool and gastric lavage. These latter materials have to be injected first into mice and recultured. It is simply impossible to suspect histoplasmosis in every infection, but, so long as we don't do it, we will miss cases.

In regard to this case, one would have difficulty saying if this is a terminal dissemination or if the organisms have been present for some time. Obviously the only answer would be a report of a biopsy taken previously. This we do not have.

Superficial Basal Cell Epithelioma Successfully Treated with Low-Voltage X-Ray Therapy: Report of Two Cases. Presented by DR. D. J. KINDEL and DR. FORMAN FRIEND.

A. P., a 76-year-old white man, was first seen in July, 1949, with a large crusted scarred area on the right scapular area. The lesion had been present for nine years and measured about 5 by 7 in. (12.70 by 17.78 cm.) in size. Biopsy showed a typical superficial basal cell epithelioma, and a wide surgical excision was performed.

In September, 1951, the patient was seen again with a recurrence at the edges of the surgical excision. Biopsy was repeated, and the area was treated with low-voltage x-ray therapy, 6,000 r being administered as a single dose.

After the reaction had subsided and healing completed, a biopsy from the original site was performed and showed no evidence of malignancy.

J. W. H., a 75-year-old white man, presented himself, with multiple lesions scattered over the trunk and face of 15 years' duration.

The largest lesion, located on the left scapular area, was elevated and crusted. Biopsies revealed a superficial basal cell epithelioma. This lesion was treated with conventional x-rays with a half-value layer of 0.8 mm. Al was administered in fractional doses to a total dose of 2,450 r. Low-voltage x-ray therapy was also given as a single dose of 6,000 r.

The other lesions, being more superficial in type, were treated with the low-voltage therapy in single doses of 6,000 r each.

DISCUSSION

DR. FRIEND: The purpose of presenting these two cases is not to advocate this form of treatment for superficial basal cell epithelioma but as an additional modality in the treatment. Many more cases over a longer period of time must be observed before a good evaluation of this treatment can be made.

The factors used in the low-voltage therapy were as follows: Dr. Kindel and I used 15 kv. with a half-value layer of 0.06 mm. Al. All lesions were treated with 6,000 r delivered as a single dose. The erythema begins within a day or two, and the reaction reaches its peak in three weeks. Healing is complete in about six to eight weeks.

The cosmetic results, we believe, are excellent, and there have been no recurrences in either patient to the present date.

Lupus Erythematosus Treated with Vitamin B_{12}: Acute Systemic Lupus Erythematosus; Chronic Discoid Lupus Erythematosus. Presented by DR. SAMUEL GOLDBLATT.

R. C., aged 25, a white married woman, presents an eruption which began on her forehead and cheeks in August, 1949. There was a sudden exacerbation involving her face and left upper arm in November, 1950. The patient had been treated as having an erythema multiforme.

When first seen April 27, 1951, she stated that an explosive eruption began two weeks before, immediately after exposure to sunlight. She had missed her menstrual period for five days.

Examination revealed erythematous, urticarial, scaly, vitiginous, and hyperpigmented lesions involving the skin of the entire body, except for the anterior chest and breast area, which was covered by the bra. The biceps, supinator, and upper abdominal reflexes were not elicited. Pulse rate was 104; there was a 30% reduction in vibratory sense. The mucous membranes were normal.

Treatment was begun on March 5, 1951, with intramuscular injection of crystalline vitamin B_{12}. The doses were administered three times weekly and varied from 15 to 120 γ per dose. The patient improved considerably with each injection.

On June 24, 1951, the patient again exposed herself to excessive sunlight and became immediately dizzy and complained of general malaise. The skin areas which had previously remained clear now developed typical erythematous lesions. After two injections the toxic manifestations disappeared. The lost reflexes were regained, and vibratory sense was elevated to far above normal levels.

On Oct. 5, 1951, the patient was admitted to the hospital for bleeding placenta praevia and was discharged after two days. On Dec. 28, 1951, she delivered a 7 lb. 14 oz. (3.5 kg.) boy. After delivery, treatment was administered only once a week, and one month afterward she began to have lesions suspicious of the discoid type under the left eye and along the lower jaws. Resumption of treatment three times a week caused a notable regression of the recurrent lesions.

Biopsy was compatible with the picture of lupus erythematosus.

S. G., aged 54, a white married man, presented lesions over the right eyebrow and on the bridge of his nose late in 1949. After six bismuth injections the lesions almost completely healed. Following an almost immediate recurrence of the lesion on the nose, it was destroyed by electrocautery, with immediate recurrence again.

On examination the patient showed a recurrence of all the original lesions plus several new deep indurated lesions on the scalp, eyebrows, nose, and zygomata. The lesions were circinate and serpiginous and in the preauricular areas were verrucous.

Crystalline vitamin B_{12} therapy, 120 γ intramuscularly twice weekly, was introduced in November, 1951. The patient immediately noted an increased feeling of well-being, and the color elevation and induration of the lesions began to regress. Under treatment there has been a consistent improvement in the general physical condition, as well as in the local lesions.

Biopsy showed lupus erythematosus, discoid type.

DISCUSSION

DR. FRIEDLANDER: I have had several patients with cases of discoid and subacute types, with good responses to injections of vitamin B_{12}.

DR. GOLDBLATT: During an investigation of the response of the vibratory sense in various diseases to possible therapeutic agents, it was found that the intramuscular administration of crystalline vitamin B_{12} caused a dramatic and sustained elevation of the pallesthetic levels in patients with lupus erythematosus. Accordingly, in March, 1950, I undertook a systemic study of the therapeutic effect of vitamin B_{12} in the various phases of lupus erythematosus.

It was found that vitamin B_{12} was tolerated in doses ranging from 15 to 1,000 γ. Even the larger amounts were given daily for long periods of time, without toxic or allergic reaction. In adequate dosage vitamin B_{12} rapidly relieved systemic symptoms, promoted involution of skin lesions, elevated the depressed levels of vibratory sense appreciation, and helped to correct hematologic abnormalities. Healing of the skin eruption was accomplished without residual scarring, atrophy, or pigmentation.

Small doses of vitamin B_{12} (15 γ at weekly intervals) were effective in the healing of discoid lesions. Increased dosage (100 γ daily or three times a week) will probably increase the speed of recovery. For acute dissemination or severe and extensive recurrences, daily treatment should be started with doses of 100 to 1,000 γ for one to two weeks. Maintenance therapy in all phases of lupus erythematosus should be continued for several months after complete healing of the skin lesions, preferably until the pallesthetic sense and the blood picture are restored to normal values.

Fatigability, lassitude, and pallhypesthesia were rapidly relieved by this treatment both in the original and the recurrent state of the disease. Skin lesions involuted promptly without respect to the failure of previous treatments. The depth and induration of the individual lesion was the most important determining factor in the rate of healing. Restitution of the integument under this therapy was without scarring or atrophy, and the pigmentary disturbances of the subacute and acute disseminated phases of the disease eventually yielded normal skin coloration. The secondary anemia cleared much more slowly than the skin eruption; here the erythrocyte count improved first, then the hemoglobin content, and finally the abnormal differential white blood cell count. Recurrences during and following therapy were usually precipitated by solar or ultraviolet ray exposure. They included the ordinary discoid type lesions, as well as a hitherto undescribed urticarial eruption limited to the areas of previous erythematous involvement. All recurrences of any type yielded to further treatment with vitamin B_{12}. In the presence of anemia or if the levels of vibratory sense appreciation have not been stabilized at normal or above normal values, treatment should be continued until stabilization is achieved. Regressive changes in the blood picture or depression of the levels of vibratory appreciation below normal values occurring after cessation of therapy are regarded as probable precursors of relapse. Vitamin B_{12} therapy is to be resumed in these circumstances.

Vitamin B_{12} is an effective nonhazardous agent for the treatment of all types of lupus erythematosus producing involution of dermal lesions, regression of systemic symptoms, elevation of pallhypesthesia, and correction of the anemic blood picture.

Investigative Studies in an Eczematous Contact Dermatitis from Coal Tar. Presented by the DEPARTMENT of DERMATOLOGY and SYPHILOLOGY, CINCINNATI GENERAL HOSPITAL.

For approximately 40 years this patient has had varicose veins. During the past year she had been bothered with an erythematous scaling area of dermatitis located on the lower third of her right leg and instep. On Oct. 16, 1952, she was seen in the clinic, and a 5% crude coal tar ointment was prescribed. Shortly following application, there developed a marked burning sensation, and the ointment had to be removed. On Oct. 22 she was seen again and was admitted to the hospital because of the increasing severity of her dermatitis, which had now become intensely erythematous, edematous, and exudated. There was also a papular dermatitis which developed on the flexor surfaces of her forearms. On the soles of her feet there was a pruritic scaly dermatitis, the scrapings of which were negative for fungi. Cultures were not reported. During the course of testing, the patient developed a dry erythematous dermatitis of her thighs, buttock, and lower abdomen, which was possibly due to irritation from rubber sheeting and bed linen.

Patch tests were as follows: 3% crude coal tar in liquid petrolatum, 2+; 10% shale oil in zinc oxide paste (Lassar's zinc paste), 1+; 3% ichthammol (Ichthyol) in zinc oxide paste, negative; patch tests to above bases, negative. Some of the fractions of shale oil gave the following results: heavy distillate (pure), 2+; residuum uncracked (pure), negative; residuum cracked (pure), negative. On the right side of the back the results for the aromatic fractions of coal tar were as follows: xylene (50% in liquid petrolatum), negative; toluene (50% in liquid petrolatum), negative; benzene (50% in liquid petrolatum), negative; pyridine (50% in water), negative; anthracene (50% in benzene), positive; phenanthrene (50% in benzene), positive; quinoline (50% in benzene), positive. These positive tests were thought to be due to irritative effect of benzene. A patch test with pure benzene was positive (left arm). Therefore, repeat patch tests with pure anthracene powder, pure phenanthrene powder, and 50% quinoline in alcohol were applied and were negative.

DISCUSSION

DR. ROBERT BRANDT: True sensitivity to coal tar is rare. Sulzberger and Baer are even of the opinion that cases considered so are often caused by the increased sensitivity to light under tar treatment. In the cases discussed today, however, light has no share. Which parts of the tar are responsible is not easy to decide, because tar is a mixture of many chemical compounds, not all of which can be easily isolated. In order to narrow the number of suspected substances, skin tests were also done with Colorado Shale Oil. This oil belongs in the "tar group" but is not identical with coal tar, only overlapping in its composition. According to

whether the results of the skin tests with the two materials are identical or different, we may conclude that the sensitizer must be looked for in the compounds that are either common to the two or particular to one.

Comparative testing was also done with shale oil fractions of different boiling points, which should permit us to determine whether the sensitizer is among the low-boiling compounds, which are primary irritants, or the high-boiling ones, which are more therapeutically effective (and also more carcinogenic).

In one case the patch test with whole crude oil was positive, with the fractions negative. This can be explained by the fact that the sum of the fractions is not completely identical with the whole oil and because of breaking up and new formation of compounds under high temperatures during distillation.

DR. A. H. LANCASTER: Coal tar sensitization in my patients is very common. Coal tar is a good drug, but it is dangerous; the effects are definitely worse when the patient gets in the sun.

Nickel and Cobalt Hypersensitivity. Presented by the DEPARTMENT of DERMATOLOGY and SYPHILOLOGY, CINCINNATI GENERAL HOSPITAL.

R. A., a 32-year-old white woman, had skin lesions which began about two months before admission to the hospital, when there developed a pruritic papular eruption of the left wrist in the area where she had been wearing a metal wristwatch band. The lesion remained localized for several weeks but became generalized.

The patient has had one previous episode of dermatitis during her pregnancy 12 years ago. There is no other history of previous skin lesions.

On admission to the hospital she had a generalized eruption involving all extremities, neck, and back. The lesions were erythematous, papulopustular, oozing, and crusted.

During her hospital stay she has been treated with intravenous injection of 10 mg. of corticotropin (ACTH), followed by 15 mg. intramuscularly for five days and topical therapy, with slow improvement.

Laboratory studies were as follows: hemoglobin 16.6 gm.; white blood cells 18,600, with polymorphonuclear leucocytes 60%, lymphocytes 17%, monocytes 11%, eosinophiles 11%; urine negative; fasting blood sugar 67 mg. per 100 cc.

Patch tests were as follows: nickel sulfate (5%, impure, contains cobalt [?]), 2+; pure nickel (metal), 3+; nickel coin, 2+; nickel sulfate (5%, cobalt-free), 2+; Inconel stainless steel (75% nickel), negative; stainless steel (8% nickel, 18% chrome, 74% iron), 1+; cobalt nitrate (5%, impure, contains nickel?), negative; cobalt chloride (2%, 1% nickel), 2+; cobalt nitrate (5%, 0.05% nickel), 2+; cobalt chloride (2.5%, nickel-free), 3+; cobalt chloride (1.25%, nickel-free), 3+; cobalt sulfate (2.5%, nickel-free), 1+; cobalt oxalate (5%, nickel-free), negative; vitamin B_{12}, negative; potassium iodide (25%), 3+; tincture of iodine (3.5%), 2+; thimerosal (Merthiolate [1:1,000]), 1+; potassium dichromate (0.5%), negative; chromium chloride (2%), negative; mercury bichloride (0.1%), negative; phenol, negative; paraphenylenediamine (2%), negative; Duponol C, 1+; Woodbury soap (1%), negative.

DISCUSSION

DR. BIRMINGHAM: The results of the patch tests with nickel and cobalt salts on this patient are, to say the least, confusing. For many years dermatologists and others interested in cutaneous allergy have tried to demonstrate a correlation between nickel and cobalt in terms of cross sensitivity. There is logic in the thought because of the close occurrence of nickel and cobalt in the periodic table.

Investigators performing these tests have concluded that some patients who are sensitive to nickel are also sensitive to cobalt. Frequent mention has been made of the use of chemically pure test materials. We have found that the term "chemically pure" can be a misnomer. Most of these American Chemical Society-labeled materials actually contain traces of the related metal. For example, so-called laboratory-pure cobalt may contain up to 0.2% nickel and vice versa. Attempts to demonstrate true cross sensitivity, therefore, are confusing, because we cannot be certain that the test materials are pure, and, if they are not, we are actually patch testing with some nickel when we patch test with cobalt.

It is extremely difficult to obtain pure compounds, but we have attempted to do so in the Division of Occupational Health Laboratory. On the first run through the spectrograph it appeared that the nickel had been eliminated from the cobalt, but subsequent spectrographic tracing showed nickel to be present in the cobalt in the order of 0.005%. This patient was patch-tested with some of this ostensibly pure cobalt. When we patch test with cobalt containing small amounts of nickel, we cannot say that the positive reactions to cobalt in a nickel-sensitive patient are true cross reactions. When we can be certain, however, that we are dealing with a cobalt compound which does not contain nickel, we can state that cross sensitivity is probably the cause of a positive reaction to cobalt in a nickel-sensitive patient.

Mycetoma Caused by Rhizopus. Presented by the DEPARTMENT of DERMATOLOGY and SYPHILOLOGY, CINCINNATI GENERAL HOSPITAL and (by invitation) DR. GAIL S. ENGLANDER.

This 6-year-old white boy was admitted to the hospital because of severe sepsis associated with an infected tooth. The skin lesion was noted on admission. This lesion was of three years' duration, was present on the axillary border and chest wall. The parents believed this developed after an insect bite. Two years ago a specimen taken for biopsy was diagnosed by Dr. Hamilton Montgomery as being compatible with granuloma annulare. The border of the lesion consists of active lichenoid papules. The center of the lesion is reticulated and atrophic. There are no sinuses. The child also had a hepatosplenomegaly.

Laboratory studies gave the following results: hemoglobin within normal limits; urogram within normal limits; Kahn test, negative; chest x-ray, normal chest; tuberculin, positive; histoplasmin, negative; mycologic culture (from skin surface), Rhizopus; biopsy, (*a*) atrophic center of lesion, (*b*) active border of lesion.

Essentially the biopsy reveals an extensive granuloma extending deep into the panniculus, with foreign body giant cell response. Schiff periodic stain emphasizes the huge nonseptate mycelia in the center of these masses. The advancing peripheral border, as well as the atrophic center, shows these masses. The child has been resistant to all forms of therapy.

DISCUSSION

DR. ASHTON WELSH: This is a most unusual type of lesion. Although there were a number of giant cells, Dr. Montgomery believed the lesion to be an atypical granuloma annulare when a specimen for biopsy was taken several years ago. No fungus elements were present then. The lesion receded 80% on large oral doses of one of the pantothenic acid derivatives plus vitamin E. The picture has changed now. The child has scratched his lesion and at times has had secondary infection in it. Since this lesion was clinically and histologically granuloma annulare originally, I wonder if the present fungous infection is in the nature of a secondary infection in a lesion of granuloma annulare.

DR. LEON GOLDMAN: When we first saw this lesion I did not know what it was. The main elements were an active border of brown, slightly scaling lichenoid papules and an atrophic center. We asked for several deep specimens for biopsies, because we suspected a peculiar atrophoderma. Fungus cultures were asked for merely to complete the work-up of the case. When I heard about the biopsy, I still could not believe this type of lesion could be a mycetoma. It is interesting to speculate about the associated hepatosplenomegaly, but without a biopsy of a specimen of the liver it is pure speculation. With the atrophic condition, the activity, and the presumed organism, I do not believe chemotherapy, either iodides or dihydroxystilbamidine, will be effective. The surgeon tells me he can do plastic surgery fairly easily. I would recommend this, even with the hepatosplenomegaly unexplained. (Note: Later, the hepatosplenomegaly disappeared completely and was in all probability associated with the tooth infection. The mycetoma has not improved and will be removed surgically.)

DR. JAN SCHWARZ: The culture from the surface is Rhizopus. Until we get a culture from the tissue we can only assume that the nonseptate mycelia deep in tissue also represents Rhizopus. From a survey of the literature I can find no report of a lesion of this appearance caused by a Mucor or Rhizopus. Pulmonary lesions of this type have not responded to iodides.

Sweating Studies in a Case of Psoriatic Erythroderma Under 17-hydroxycorticosterone (Comound F) Therapy. Presented by the DEPARTMENT OF DERMATOLOGY AND SYPHILOLOGY, CINCINNATI GENERAL HOSPITAL.

M. F., a 42-year-old white man, had scaly palms and soles about two and one-half years ago. Subsequently, a red scaling eruption appeared in the inguinal areas and on the thigh. This gradually spread to involve his entire cutaneous surface, the face being affected last. He consulted numerous doctors from coast to coast but did not respond to therapy. Treatment has included pancreatin, low-fat diet, protein hydrolysates (Amigen), complete extraction of upper teeth, cortisone, corticotropin (ACTH), oxytetracycline (Terramycin), vitamin B complex (Becotin), crude liver extract, iodochlorhydroxyquin (Vioform ointment), cholecystectomy, arsenic, penicillin, and psychotherapy. From November, 1951, until admission here in May, 1952, he had been on a maintenance dose of 125 mg. of cortisone acetate per day, with mild relief. Exacerbations had occurred on reduction to 75 mg. of cortisone acetate per day.

On examination the entire cutaneous surface is fiery red and moderately scaly. Skin lines are exaggerated, and all nails are dystrophic. Tongue is fissured with hypertrophied papillae. Liver edge is palpable 1 fingerbreadth below right costal margin. Spleen is not palpable.

Laboratory data were as follows: Kahn test negative, red blood cells 4,450,000, hemoglobin 16 gm., hematocrit reading 48%, reticulocytes 2.0%, platelets 347,000, mean corpuscular volume 108 cu. μ, mean corpuscular hemoglobin 35 $\gamma\gamma$, white blood cells 9,100, neutrophiles 80%, eosinophiles 4%, lymphocytes 14%, monocytes 2%, eosinophile count 242 per cubic millimeter, blood urea nitrogen 7 mg. per 100 cc., sodium 134 mEq. per liter, potassium 3.65 mEq. per liter, carbon dioxide 32.5 mEq. per liter, electrocardiogram normal, thymol turbidity 1 unit, cephalin-cholesterol flocculation negative, total lipid 550 mg. per 100 cc., bilirubin 0.1 direct (0.3 total), alkaline phosphatase 2.9 Bodansky units, total protein 5.70 gm., albumin 3.50 gm., globulin 1.60 gm.

Biopsy of a specimen of the skin showed psoriasis. Biopsy of a specimen of an axillary node was normal. Numerous intradermal injections of hydrocortisone (Hydrocortone) acetate (17-hydroxycorticosterone [Compound F]) in concentrations of 0.25 to 25 mg. caused blanching and cessation of scaling at the site of injection. Detailed biopsies revealed absence of psoriasis in the local areas of injection. Injections of cortisone were without result. Various types of 17-hydroxycorticosterone ointment produced no response. Intradermal epinephrine (Adrenalin) caused normal immediate response with blanching, but the deeper vessels responded slowly. Temperature regulation aberrations were studied at the Kettering Laboratory. They revealed grossly inadequate response of his cutaneous blood vessels to temperature changes, parasympathomimetic and sympathomimetic stimuli. The cutaneous blood vessels remained dilated at temperatures which were below the zone of thermal neutrality and at which temperature the patient shivered. The patient continued to shiver when the ambient temperature was brought up to 95 F. Epinephrine caused normal immediate response of capillaries, but deeper vessels responded slowly or not at all. Sweat function in all areas could not be demonstrated by local injections of methacholine (Mecholyl) chloride or by thermal stimuli.

Therapy used during present hospitalization was as follows: corticotropin, 10 mg. by intravenous drip and 10 mg. intravenously at midnight from May 21 to July 23; cortisone acetate, 25 mg. from May 21 to May 25 and June 27 to June 28; dimenhydrinate (Dramamine), 50 mg. at bedtime as a sedative; potassium chloride, 3 gm. a day; vitamin A palmitate (synthetic), 240,000 units a day orally from July 7 to July 30; 17-hydroxycorticosterone, 15 drops three times a day orally from July 24 to July 27; cortisone acetate, 15 drops twice a day from July 28 to July 30. Among the topical applications for lubrication of the skin were an oxycholesterol-petrolatum ointment base (Aquaphor), Vi Dom A, Vanibase (cetyl and stearyl alcohol, sodium lauryl sulfate, white wax, and propylene glycol), petrolatum, an oil-in-water emulsion base (Neobase), Multibase, coal tar solution (Liquor Carbonis Detergens), vitamin A ointment, and 3% iodochlorhydroxyquin (Vioform ointment). Later oral 17-hydroxycorticosterone (80 to 100 mg.) was used, with maintained good results. In addition, the patient was under detailed psychiatric management by the Department of Psychiatry. At first the patient was hostile; later he welcomed the interviews.

Hospital Course.—The patient began improving on about July 9. The fiery redness faded first on his scalp, and the scaling decreased. Improvement spread downward to involve his neck, arms, and trunk. Freckles began appearing on his upper back and arms. He has continued to slowly improve since then. Sweat function and normal vascular responses returned slowly, with gross clinical improvement.

Course after Discharge.—He was discharged finally, with treatment by 17-hydroxycorticosterone (80 to 100 mg. daily) and bland local therapy. The redness persisted; the scaling also persisted, chiefly on the legs and palms, but the trunk, face, and scalp were clear. The patient is active in a regular job.

DISCUSSION

DR. R. R. SUSKIND: This patient is a most interesting subject for a study of altered vascular responses and sweat function in cutaneous disease status. When he was first admitted to the hospital in May, 1952, we were not able to stimulate sweating either with methacholine (Mecholyl) chloride or with heat. When we injected epinephrine locally, there was only blanching of the capillaries locally but no constriction of the deep vessels, i. e., the subpapillary vessels. In June we repeated the same tests and induced axillary sweating with injections of methacholine chloride but not with heat. At this time, too, we found that he was not able to tolerate certain ordinarily comfortable environments. In the nude state, ambient temperatures of 85, 90, and 95 F. caused the man to chill. He had tremendous heat loss from widely dilated capillaries and deeper vessels, which, incidentally, did not respond to local applications of cold.

In early July, following clinical improvement, sweat function returned to some degree in isolated areas. The cutaneous vessels were still markedly dilated. At that time he was able to tolerate 100 F. and felt comfortable without much sweating at all. Even at 113 F. he felt very comfortable at first, until his rectal temperature rose.

At the end of July, however, moderate sweating from the forehead, axillae, and abdomen could be induced at 90 F., and at 100 F. generalized profuse sweating could be induced.

Histologically, sweat glands do not appear to be altered in psoriasis. Perhaps the thick parakeratosis in psoriasis may plug the sweat ducts. There is no histological evidence of this so far.

Since that time the sweat and vascular responses of this patient have coincided well with the patient's clinical status, declining when exacerbations occur locally or generally and returning when clinical improvement is noted.

This subject has stimulated interest in the study of sweat function in psoriatics. We have now demonstrated to our satisfaction that local sweating with parasympathomimetic or thermal stimuli cannot be induced within active psoriatic lesions, lesions from which the parakeratotic scale has been removed, and in many instances normal-looking healed sites.

DR. LEON GOLDMAN: This man presented a homme rouge type of psoriatic erythroderma, which was established by biopsy. It is indeed curious that the prolonged corticotropin and corticosteroid therapy over a period of time gave him no demonstrable reactions as yet. Recent x-ray of the chest and long bones gave negative results. His skin was a good medium for establishing the local inhibitory effect of various corticosteroids; the best was of course hydrocortisone acetate both on injection with the syringe and needle and with the Hypospray jet injection apparatus. Inunction of ointment, tattooing, or even sandpapering the hydrocortisone acetate into the skin had no local effect. As has been noted before, prolonged corticosteroid therapy is needed in the therapy of psoriatic erythroderma. This patient is now active, markedly improved, but still not well. The psychiatrist has been extremely helpful in the management of this patient and has assisted in the return of one who was a recluse and an invalid to an active interest in the community.

Familial Congenital Ichthyosiforme Erythroderma. Presented by DR. A. L. WELSH.

Parapsoriasis Type of Xanthoerythroderma Perstans. Presented by DR. HARRY A. NIEMAN.

Visceral Sarcoidosis Treated by Splenectomy (Two Cases). Presented by DR. EDWIN HIGGINS and (by invitation) DR. CARL W. KUMPE.

Chronic Moniliasis of the Mouth with Leucoplakia and Epidermoid Carcinoma. Presented by the DEPARTMENT of DERMATOLOGY and SYPHILOLOGY, CINCINNATI GENERAL HOSPITAL.

Generalized Lichen Sclerosus et Atrophicus of Twenty Years' Duration. Presented by DR. WINSTON U. RUTLEDGE.

Benign Familial Pemphigus (Two Cases): Biopsy Typical of Darier's Disease. Presented by DR. BETTY OWENS.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Marion B. Sulzberger, M.D., *Chairman*

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Feb. 3, 1953

Perifolliculitis Capitis Abscedens et Suffodiens. Interstitial Keratitis. Presented by Dr. F. P. Lowenfish for Dr. E. Wilkiser Ehrenreich.

R. P., an American Negro man, 28 years of age, complains of a "bumpy" eruption on the scalp, with suppuration and hair loss of 18 months' duration; he has had cloudy vision for the last 4 to 5 months.

The patient was admitted to City Hospital in May, 1952, because of his scalp condition. In the course of the routine laboratory tests the serological reaction for syphilis was found to be positive. Several weeks later, while he was being given antisyphilitic treatment, his left eye began to trouble him. During the last week of January, 1953, his right eye became involved also.

Nine years ago, while he was in the Army, the patient also had a positive serological reaction and was treated with intravenous injections of unknown nature. His service was regionally confined to the U. S. Upon his discharge he worked as a chauffeur, without any medical complaints until 1952.

The patient says he has no knowledge of a prenatal or acquired infection with syphilis. His parents died long ago of unknown causes.

Scattered densely over the vertex, the frontal, and the parietal aspects of the scalp are numerous solid or fluctuant hairless nodules, 0.5 to 3 cm. in diameter, confluent or connected with each other by firm keloidal ridges. The occipital region presents many atrophic scars, while near the nape of the neck several sausage-shaped tubular elevations are noted. With pressure, many openings in the fluctuant swellings give way to a seropurulent discharge. Introduction of a probe shows that many nodules are connected with each other through sinus formations of several centimeters.

Cervical lymphadenopathy is not present.

The following is a description of the eye condition by an ophthalmologist: Left eye (as observed since August, 1952): "There is a corneal infiltration extending from about 11 to 1 o'clock in the left eye. The fundus reveals exudative patches at the extreme periphery in the temporal inferior quadrant, with scattered pigmentations. The pupils are normal." Right eye (as observed for the first time on Jan. 30, 1953): "There is an infiltration of the cornea extending from 10 to 1, and there are fresh exudates in the extreme superior periphery of the right eye field, with scattered pigmentations.

Diagnosis: chorioiditis and interstitial keratitis."

The patient's hearing is normal. He has a high palatine arch.

Laboratory examination gave the following results: The serological reaction for syphilis was repeatedly 4+. The VDRL test was positive 1:80. The cerebrospinal fluid examination gave negative results in all respective tests. The urine was normal. A complete blood cell count and a study of the blood chemistry gave normal results. Bacteriologic examination of pus from scalp revealed Staphylococcus aureus (nonhemolytic Staphylococcus). Sensitivity to chlortetracycline (Aureomycin), oxytetracycline (Terramycin), and penicillin was observed.

The following is the biopsy report by Dr. G. Machacek: "The section seems to represent a portion of an intracutaneous epithelial cyst surrounded by granulomatous tissue."

The patient received 60,000,000 units of penicillin, bismuth subsalicylate, streptomycin, chlortetracycline administered orally in large quantities, and oxytetracycline administered orally. He also had one course of fever therapy. He received local therapy in the form of manual evacuation of pus from scalp lesions, and application of wet dressings and antibiotic ointments to the scalp, and cortisone administered subconjunctivally.

There is little improvement in the scalp condition. There is no change in the serologic reactions for syphilis.

DISCUSSION

DR. HELEN CURTH: I was very much intrigued by the forehead of this patient, which he cannot unwrinkle. If this condition would date back to the last year when the scalp condition developed I would understand that he is mechanically unable to unwrinkle the forehead because of scar formation of the scalp. He claims, however, that he has been born that way, and that as a child he was already unable to unwrinkle the forehead. Dr. Ehrenreich should consult some pictures or photos of the patient when he was a child. I am wondering if this perhaps could be cutis verticis gyrata or pachydermoperiostitis. If the patient has these conditions we should watch for internal tumors, acromegaly, and especially pulmonary disease. He has no clubbing of the fingers, and there is no familial involvement.

DR. DAVID BLOOM: The patient now presents scars resulting from his perifolliculitis, which I believe appears cured. I wonder why this patient has received as much as 60,000,000 units of penicillin, and I suspect that this enormous amount has been given because of the erroneous belief that the patient still has the infection.

DR. WILLIAM CURTH: I am interested in the question of interstitial keratitis in this patient. Does Dr. Ehrenreich think that this man has congenital syphilis? The titer is rather high —1:80.

DR. NATHAN SOBEL: I agree with Dr. Curth that when there is an interstitial keratitis the probability is that the man has congenital syphilis on that one point alone, because interstitial keratitis is so rare in the acquired form. It has been reported as occurring very rarely in acquired syphilis, but I have never seen it in acquired syphilis.

DR. F. P. LOWENFISH: I do not see why this cannot be a late congenital interstitial keratitis. The keratitis began about a year ago as a unilateral condition and then spread to the other side, which is characteristic. It is well known that late congenital syphilis usually occurs in patients between the ages of 5 and 16 years. It can begin as late as 30 years of age. This man is 28 years of age.

DR. GERALD F. MACHACEK: Without a doubt activity persists in the scars and is due to a foreign-body reaction. These foreign bodies consist of epidermis with its keratin. Such specimens for biopsy as were obtained showed evidence of active granulation-tissue formation. Although the lesions are quiescent at the moment they are not healed. Dr. Ehrenreich will consider the question of interstitial keratitis, from which this patient suffers.

DR. A. N. DOMONKOS: I agree with the diagnosis as presented on the scalp, and I only want to cite a case which we have been following for at least four or five years, in which the disease is very severe. The patient has had the gamut of all antibiotic therapy, plus x-ray epilation of the scalp. I must say that the lesions clear up for a while and then there is a recurrence. It is a very serious problem, recalcitrant to all forms of therapy.

DR. CHARLES WOLF: I want to offer suggestions as to treatment. The patient has two diseases, so-called syphilis, whether congenital or not remains to be proved, and a staphylococcic infection. Measures for the treatment of syphilis have been tried without avail, and the perifolliculitis has also been treated. What other steps or measures should be taken to immunize this person or to give him a measure of relative cure? I do not think the fact that the interstitial keratitis is present stigmatizes the person as a congenital syphilitic. Interstitial keratitis can be caused by other infections. It may be a manifestation of focal infection occurring late in life, and in regard to other stigmata of congenital syphilis being absent I think that the man does not have congenital syphilis. I would suggest, however, the use of fever therapy, or foreign-protein therapy like milk, or typhoid injections to see whether a measure of improvement can be procured, as well as x-ray therapy to the scalp.

DR. MARION B. SULZBERGER: What sort of x-ray therapy to the scalp? Epilating?

DR. CHARLES WOLF: I would give him stimulating doses. I would give him over the most infectious areas about 100 r filtered with 1 mm. of Al or even 3 mm. of Al and a total of about 1,200 r over a period of seven to eight weeks.

DR. E. WILKISER EHRENREICH: Cutis verticis gyrata is a good observation because the scalp lesions near the nape of the neck look very much like it. However, it has been reported that in advanced stages of dissecting cellulitis as well as in other long-standing pustular infections of the scalp a condition simulating cutis verticis gyrata of the nevoid or of the pituitary dermadrome type may occur. We shall never be able to obtain a picture of this patient as a child, because

the man does not know anything about his childhood. He has not known his parents, brothers, or sisters, or anybody in his family. The scalp lesions are definitely pathognomonic for perifolliculitis capitis abscedens et suffodiens.

As far as his eye condition is concerned we do think that this patient may very well have late congenital syphilis. His high palatine arch is only a minor stigma. His skeletal development which impresses me as being rather gigantic may or may not speak in favor of prenatal syphilis. However, interstitial keratitis by its own merits, according to Stokes, is so overwhelming an event in late congenital syphilis that in the light of the long-standing positive serological reaction it appears to be of paramount diagnostic value in this case. As Dr. Sobel has already pointed out, the patient's age at the onset of his eye disorder is not in conflict with the diagnosis of prenatal syphilis. Moreover, Stokes has stated that interstitial keratitis due to congenital syphilis has not infrequently appeared after initiation of antisyphilitic treatment in an asymptomatic patient with positive serological reactions. This has happened to our patient. Of course, the patient ought to have a Treponema-immobilizing test, but so far it could not be done for economical reasons.

As to treatment, the patient has had fever therapy of seven bouts with typhoid and has not reacted to it at all. The excessive dose of 60,000,000 units of penicillin was given to him only by accident before I came on service at City Hospital. Such accidents will happen in understaffed hospitals.

The suggestion that the eye conditions may be secondary to the patient's scalp affliction concurs with the experience of our ophthalmologists, who have often observed interstitial keratitis to be secondary to a primary focus in the body. The mechanism involved would be either by way of toxicity or by contiguity from a chorioiditis which the patient also has.

It is planned to give the patient another course of fever therapy, and the suggestion of x-ray together with manual therapy for the scalp condition will be considered.

Adenoma Sebaceum. Presented by Dr. Gerald F. Machacek.

M. B., white Maltese boy, aged 7, has an eruption on the face, forehead, and trunk. The mother states that her boy has had brownish-reddish spots on the left forehead since birth. When he was 6 months of age, she noticed yellowish-white to brownish-red pimples on the cheeks and nasolabial folds. Later, other spots appeared on the face and back. The scars on the chest are from old burns.

Over the cheeks, the sides of the nose, and the chin are many yellowish-white to brownish-red pinhead- to split-pea-sized papules. In between and running over these lesions are fine telangiectatic vessels. Discrete brownish and yellowish papules are seen over the forehead. There are circumscribed slightly raised firm yellow plaques, with a furrowed surface over the left and right side of the forehead and the left temple region. The upper lip presents a pea-sized nodule. Nevoid structures are disseminated all over the trunk and follow the intercostal regions. Over the right deltoid is a white plaque resembling nevus anemicus.

Biopsies of specimens from several sites revealed perivascular infiltration, fibrosis, increase in atypical hair follicles, and increase of sebaceous cells. A tiny nevus pigmentosus was present over the outer deltoid area.

X-ray examination showed calcifications near the lateral ventricles that are compatible with calcifications usually found in tuberous sclerosis.

Electroencephalogram revealed abnormal activity suggestive of a convulsive disorder.

DISCUSSION

Dr. Juan Larralde: Most of the patients I have seen with this condition have a normal intelligence. How frequently is a low mentality in this type of condition found?

Dr. Marion B. Sulzberger: How frequently is impairment of the intelligence found in Pringle's adenoma sebaceum?

Dr. H. Goodman: Only in the books.

Dr. David Bloom: From my own experience and from the reports in the literature I have the impression that about 50% of the patients with adenoma sebaceum have mental deficiency.

DR. HELEN CURTH: I agree with Dr. Bloom.

DR. F. P. LOWENFISH: I ran across something in the text recently which said that renal tumors are found in about 80% of the cases.

DR. MARION B. SULZBERGER: Adrenal or renal?

DR. F. P. LOWENFISH: Renal. In reference to the renal tumors as mentioned above, in the *Transactions of the American Academy of Ophthalmology and Otolaryngology*, September-October, 1952, on page 751, on discussion of adenoma sebaceum is found the quote that renal tumors are found in 80% of the cases.

DR. CHARLES WOLF: The case as presented shows only one manifestation of adenoma sebaceum outwardly, but the interesting feature of these cases of adenoma sebaceum is the association of hemartomas of the internal organs, e.g., brain, heart, lungs, spleen, kidneys, adrenals, and eyes. One of the best monographs on the subject, "Homartial Nature of the Tuberous Sclerosis Complex," by Sylvan Moolten, covers the subject fully.

DR. GERALD F. MACHACEK: This cutaneous affliction may or may not be associated with other very serious organic developmental defects, some of them being of a malignant nature. These may be present in the central nervous system, the heart, or the kidney. A mulberry tumor may be seen near the optic disc. Epilepsy and mental deficiency may be manifest. This is a simple case with only cutaneous manifestation being seen. This patient does not show subungual or periungual fibromata, which are often present and involve both the toes and fingers. This child shows a peculiar pleomorphism of cutaneous manifestations. There was present a so-called nevus anemicus. Histologically, fibroses were seen. In the numerous biopsy specimens taken from this patient the so-called adenoma sebaceum was not evident. Pigmented nevi were recognized, but the most characteristic finding was the vascular proliferation and the multiplication of perivascular cells. I should like to add that there are brilliant people suffering from adenoma sebaceum as well as morons afflicted with tuberous sclerosis (epiloia).

Multiple Fibromata. Generalized Scleroderma? Presented by DR. JESSE A. TOLMACH for DR. LEO ORRIS.

D. N., a 55-year-old white woman, was first admitted to Beth Israel Hospital in March, 1951, with a chief complaint of constant upper abdominal pains of two months' duration. She had two bouts of hematemesis and tarry stools 7 years and 18 months previously. Globulin-insulin series at another hospital revealed a duodenal ulcer, and an ulcer regimen was prescribed. She felt well for about a year, but again began to have epigastric burning pains which became constant.

The results of physical examination on admission were negative except for the following: (1) multiple pedunculated pigmented 0.3 to 1 cm. nodules on the neck, arms, back, and abdomen, (2) tightening of the skin of the tip of the nose, upper lip, chin, and over the second and third phalanges of the fingers, with slight cyanotic discoloration.

Globulin-insulin series revealed a marked dilatation of the esophagus associated with ulceration of the lower third, marked stasis and dilatation of the second and third portions of the duodenum, and marked dilatation of the loops of the jejunum. The above changes were considered compatible with diagnosis of scleroderma.

The laboratory examinations were as follows: A urine examination gave negative results. The results of a complete blood cell count were negative. Total protein was 7.4 gm. (albumin, 3.5 gm., globulin, 3.8 gm.). The electrocardiogram showed a left bundle branch block. The sedimentation rate was 63 mm. in one hour. Esophageal biopsy revealed acute inflammation, lymphoid aggregates, and gastric glands. A chest x-ray revealed slight fibrosis in the right lower lobe. Skin biopsy revealed a fibromatous nodule with a collection of monocytic cells.

A diagnosis of generalized scleroderma was made and the lesions of the esophagus and duodenum attributed to this disease. From March 30 to April 17 she was treated with corticotropin (ACTH), with no improvement. She returned March, 1952, with swelling and tenderness of the finger joints, wrists, elbows, shoulders, and knees. This was diagnosed as rheumatoid arthritis and was treated with cortisone 50 mg. a day for about one month. Cortisone therapy was stopped because of an episode of hematemesis and melena, and she was then treated with aurothioglucose (Solganol) 50 mg. a week and this dose was continued until

November, 1952. At this time small blisters appeared on the fingertips. These have continued to appear in spite of discontinuance of the gold therapy and local medications (iodochlorhydroxyquin [Vioform], crude coal tar, aluminum acetate [Burow's]paste). The tightness of the mouth and skin of face, however, has decreased markedly in the past year.

DISCUSSION

DR. DAVID BLOOM: On first glance one is reminded of neurofibromatosis. However, I do not remember ever having seen a case of neurofibromatosis without café-au-lait spots. I would, therefore, need confirmation of this diagnosis by pathological examination.

DR. CHARLES WOLF: I should like to consider this case very interesting and obscure from the standpoint of diagnosis. The lesions per se are yellowish, fairly firm, and freely movable, and have the characteristics of xanthomata. The patient may have xanthomatosis, and the x-ray findings of the gastrointestinal tract suggest congenital hypertrophic dilation of the colon (Hirschsprung's disease). Another disease I was thinking it might be is pseudoxanthoma elasticum or leiomyoma.

DR. THEODORE H. FINKLE: I believe that Hirschsprung's disease is a childhood disease and colonic.

DR. LEO ORRIS: This woman has had tightness around her mouth and nose for the past year, which has gradually subsided. At the time of her hospital admission her major complaints were gastrointestinal. A diagnosis of generalized scleroderma was made, however, on the basis of skin and the results of the esophageal biopsies. The question at present is whether the recent lesions on her fingers are related to the generalized scleroderma, to local vascular changes, or to therapy that she has been receiving for arthritis.

Sturge-Weber Syndrome. Presented by DR. F. P. LOWENFISH.

P. D. A., a white American boy, aged 2 years 9 months, presented a port-wine stain on the left side of the scalp, forehead, left orbital area, left side of the nose, and face.

The capillary hemangioma has been present since birth. The patient is the second child to a young couple. The parents and a 3-year-old brother are living and well. The familial history is noncontributory. The pregnancy, delivery, and neonatal period were normal. The mother states that the left eye looked black and very large at birth. Careful questioning of the mother failed to reveal any history of trauma or virus infection during pregnancy. When the infant was 2 months of age the first convulsive seizure occurred, lasting one to two minutes and occurring 12 to 15 times that day. When the infant was 5 months of age, after a period of observation and unsuccessful operative attempt to reduce the pressure of the glaucoma, the left eye was enucleated. When he was seven months of age there was a convulsive period lasting one day, and the diagnosis of brain tumor was made and concurred in by a second hospital. Since then, convulsive seizures have recurred during febrile periods, but were controlled by diphenylhydantoin (Dilantin) therapy at other times. At the beginning of the second year he could not sit without support and could not talk. At present, his mental and physical abilities are that of a child 5 months of age.

There is an extensive unilateral macular nevus flammeus descending from the vertex on the left side of the head to the parietal region, left forehead, left orbital area, and the left side of the nose. There seems to be little change over the left oral mucosa, but over the soft palate the mucosa is darker and numerous telangiectodes are seen.

Laboratory examinations gave the following results: X-ray studies of the skull revealed nothing of note, and there was absence of intracranial calcifications. Electroencephalogram studies showed activity over the right hemisphere, with high-voltage slow waves. Over the hemisphere on the left side the activity was of comparatively low voltage.

A pneumoencephalogram showed extreme brain atrophy, more marked on the left side, and normal ventricular system. The findings were interpreted as diffuse cortical degeneration. There was no evidence of vascular malformation.

DISCUSSION

DR. A. N. DOMONKOS: This is the third case that I had the privilege of seeing. It is a very interesting case. My own suggestion in regard to the epileptiform seizures is to do an arteriogram of the head which might show that hemangiomas are causing these seizures.

DR. MARION B. SULZBERGER: Dr. Domonkos, could you tell us some more about the syndrome? What are its characteristics?

DR. A. N. DOMONKOS: Nevus flammeus is usually on one side of the face, and usually on that side there is some ophthalmic manifestation, a condition called buphthalmos, which is a sort of glaucomatous condition. The patients usually lose the sight of that eye in early childhood, and very frequently enucleation of the eye must be done. The epileptiform seizures are variable. In one case that I had the privilege of following for some time the patient had a ligation of one of the larger vessels, bringing about a decrease in the number of epileptiform seizures. This girl that I followed for some time is now about 26 or 27 years of age. She uses a cosmetic (Covermark), to cover the port-wine stains on her face. Her epileptiform seizures have disappeared for the last six or seven years. She is relatively well adjusted to her environment and carries on a normal social life.

DR. GERALD F. MACHACEK: This condition is similar to adenoma sebaceum in that there is no involvement of other organ systems in conjunction with the cutaneous manifestations. There may be ocular as well as meningeal and cerebral defects. This syndrome may be related to Lindau-von Hippel disease which is angioblastomatous proliferations involving the eye and causing angiocystic formations in the pancreas and other viscera. In a friend of mine the Lindau-von Hippel syndrome developed at about the age of 14. By the time he was 16 he was blind, and, later, cysts were removed from his pancreas. He died, and I discovered bone formations in one of his eyes. The condition with which we are dealing tonight is a definite, externally manifest angiomatosis of the nevus flammeus type which also involves the meninges and the brain. Cortical lesions are undoubtedly present and have caused the epileptiform seizures, with the resultant electroencephalographic deviations.

DR. H. GOODMAN: Is the nevus, the port-wine stain, associated with the syndrome? Could it come with the strawberry or vascular tumor type?

DR. GERALD F. MACHACEK: It is maintained that this syndrome is associated only with the port-wine stain. Angiography is often performed but is a definite hazard. Some of the substances which are used cause vascular changes. The picture is often confusing due to the normal vagaries of the cerebral circulation or the superimposition of the two halves of the vascular picture. The result of angiography might be interesting but I am not in favor of performing it on this child. Today's technique has been improved, and one need not use the surgical approach. I think, however, that we should limit even our scientific curiosity.

DR. FRANK E. CORMIA: Harvey Cushing wrote a monograph on the subject a number of years ago and pointed out the various types of syndromes which could occur in conjunction with epileptiform seizures. It was his impression, as I recall, that surgical measures were not very effectual. As a matter of fact, I have had the opportunity of seeing several patients, two of whom were seen by me in conjunction with Dr. Wilder Penfield. In both these patients deep x-ray therapy was tried, but without success. I think that when one makes such a diagnosis, it carries a fairly grave prognosis.

DR. F. P. LOWENFISH: Sturge, in 1879, first noted the association of facial nevus, glaucoma, and cerebral disturbance. F. Parkes Weber, in 1929 (*Proc. Roy. Soc. Med.* **22**:431-442, 1928-1929), presented the roentgenologic confirmation of the meningeal telangiectasia. That is where the syndrome of Sturge-Weber begins. It is also known as the Sturge-Weber-Krabbe disease. That is in the ophthalmological books (Duke-Elder, W. S.: Textbook of Ophthalmology, Vol. 5, St. Loius, C. V. Mosby Company, 1952, p. 5094.). Synonyms are meningocutaneous angiomatosis or encephalotrigeminal angiomatosis, which means the trigeminal nerve distribution innervating the conjunctiva and the skin on the unilateral side of the face. The other synonym is encephalofacial angiomatosis.

The syndrome and symptoms are divided into four groups as I could understand it: First is the extensive capillary angiomata of the face, that is unilateral and also involves the mucous membranes of the conjunctiva, the buccal mucosa, and the palate. Second is the angioma of the

choroid associated rather frequently with an early glaucoma, as in this child. Third is the meningeal angiomatosis with cerebral calcifications visible radiologically and leading to cortical degeneration and mental disturbances, and fourth, and final, are the neurological signs and symptoms, as focal (Jacksonian) epilepsy, on the contralateral side, hemiplegia, hemianopia, dyspituitarism, and mental deterioration. Occasionally both sides of the face are involved. There are about 200 cases reported in the literature.

Papulonecrotic Tuberculid. Presented by DR. GERALD F. MACHACEK.

T. R., a Negro American boy, aged 9, has an eruption on all extremities of six weeks' duration. The onset of the current illness began in December, 1952, with lesions being present on all extremities and increasing rapidly in number, followed by a painless rash early in January, 1953. This was not associated with fever, anorexia, joint pains, or digestive disturbances.

The lateral and extensor surfaces present numerous skin-colored or reddish nodules 2 cm. or smaller in diameter and with occasional scaling. There are also smaller papular and pustular crusted lesions scattered over the thighs and arms. The axillary, inguinal, epitrochlear, submaxillary, and cervical glands are enlarged.

Laboratory examinations revealed the following findings:

The serologic reactions for syphilis were negative. The red blood cell count was 4,200,000 and the white blood cell count was 3,400. The hemoglobin content was 12.0 gm. (82%). The differential distribution was as follows: polymorphonuclear leucocytes, 58; lymphocytes, 38; eosinophiles, 4. The sedimentation rate was 11 mm. in one hour. The albumin-globulin ratio was normal. The tuberculin test gave a negative result in a 1:1,000,000 dilution and a positive reaction in a 1:100,000 dilution. The results of a biopsy were as follows: The slides showed characteristics of erythema induratum and necrotic grandulomatous lesions somewhat resembling granuloma annulare.

The diagnosis was papulonecrotic tuberculid.

DISCUSSION

DR. H. GOODMAN: Is there any history of x-ray of the chest, Dr. Sulzberger?

DR. MARION B. SULZBERGER: I do not see any here. Was there any chest x-ray, Dr. Machacek?

DR. GERALD F. MACHACEK: Dr. Ehrenreich says that the findings were negative.

DR. ARTHUR B. HYMAN: The interesting thing about this case was that apart from the lesions that looked very much like papulonecrotic tuberculid there were numerous scattered nodules which were subcutaneous or in the deep cutis. If I remember correctly, the biopsy report was that there was some similarity to granuloma annulare.

DR. MARION B. SULZBERGER: And to erythema induratum—to both—you are correct.

DR. ARTHUR B. HYMAN: The report also indicated similarity to erythema induratum. This makes sense, in view of the association in some cases of papulonecrotic tuberculid and erythema induratum. There is an article by Felix Pincus, I think, written in the *Zeitschrift* some 15 years ago, in which he collected a number of cases of papulonecrotic tuberculid associated with granuloma annulare. Ordinarily, granuloma annulare has nothing to do with tuberculosis, but in view of the fact that there are cases of associated papulonecrotic tuberculid and granuloma annulare and transition forms, both clinically and histologically, this case would be in that group, and one might rightfully assume that the deeper lesions are indeed deep forms of granuloma annulare.

DR. MARION B. SULZBERGER: That I think was Herman Pincus.

DR. ARTHUR B. HYMAN: Thank you. I am sure that you remember the cases better than I do.

DR. H. GOODMAN: Is the number of cases of necrotic tuberculid decreasing in the city?

DR. MARION B. SULZBERGER: If you will permit me, I should like to say a few words about this case. The first point that I wanted to bring out is the point that Dr. Herman Goodman just made, and that is that we see less and less of these cases, and that is why I think that they are very well worth while presenting. I imagine that many of our students here, our residents, the younger men and women, have not seen any number or perhaps even one typical case of papulonecrotic tuberculid—and while this case is not an absolutely typical textbook picture it certainly

presents many lesions that are very characteristic. The lesions can be seen in all phases of development, from inception to involution and the typical round scar. No one with experience would hesitate to state that this is a case of papulonecrotic tuberculid on clinical grounds, if one can make the diagnosis on clinical grounds.

The second point is, of course, that this child is hyperergic to tuberculin. Such a reaction is, of course, only to be used on a statistical basis in a tuberculosis survey and never means anything as a single case. But as a group, in these cases the patients are inclined to be hyperergic to tuberculin and on quantitative testing react to dilutions greater than the dilutions required to produce reactions in the majority of people of their age in the same society at the same time.

The third point is that one does not need to find active tuberculosis in these cases. As a matter of fact, one finds active tuberculosis only rarely on the basis of clinical or roentgenologic or other findings, sedimentation rate, etc. I think that here, as so often, dermatologists have been pathfinders and pioneers and have led the way in the concept of focal infection, which is better established here in the field of tuberculids and trichophytids than in many other fields of medicine. In dermatology the manifestations of what one might call " focal infection" have been pretty well documented, and the data have been pretty well established as supporting that concept. One feature of that concept is that it is not the hot, active focus of infection that is the most likely to produce the distant manifestations. It very often is a torpid, quiescent, and not very massive or very apparent or very active focus that is most prone to cause the greatest amount of distant trouble. A second feature of the concept of focal infection which is illustrated here and in other examples in dermatology is the fact that these secondary lesions are often almost sterile; that is, the distant lesions are not filled with viable micro-organisms. Often the micro-organisms are not easy to discover or easy to culture from the lesions of ids. After a great deal of careful, diligent, searching can one demonstrate that in some cases at least the micro-organisms from a distant focus actually has traveled to the site where one sees the distant secondary lesion.

DR. CHARLES F. POST: Within the past few months I have seen two tuberculids occur under unusual circumstances. This occurred in two patients who had taken cortisone for arthritis for a long time. One patient had a lichenoid tuberculid and the other a papulonecrotic tuberculid. As you know, cortisone is contraindicated in active and inactive tuberculosis, and the eruption was the initial sign of recurrent tuberculous activity.

DR. MARION B. SULZBERGER: Did these patients have a flare-up of a real focus?

DR. CHARLES F. POST: In one patient huge tuberculous abdominal lymph nodes developed which required surgery. I have no follow-up on the other case.

DR. GERALD F. MACHACEK: I stress the fact that some of these lesions look like those of granuloma annulare. I agree with the chairman that it is often difficult to find a focus of active tuberculosis although there is undoubtedly a closed focus somewhere. Occasionally, one is fortunate to see a patient who has the manifestations of active tuberculosis, such as tuberculous adenitis and in whom at the same time papulonecrotic tuberculids, erythema induratum, or perhaps some other clinical manifestation of this curious immunologic phenomenon develops. Very often we see papulonecrotic tuberculid associated with lichen scrofulosorum. In a patient the whole gamut of tuberculids may occur, on the one hand necrotic, on the other proliferative and solid. This exanthem often comes in crops. The histology of the individual lesions varies from one of a nonspecific nature resembling a banal inflammation to a classic tubercle formation with a certain amount of necrosis. In evaluating the histology one must be careful. I have seen cases presented as papulonecrotic tuberculid which were manifestations of a chronic or subacute banal pustulosis with some granulomatosis.

DR. H. GOODMAN: Will you tell how to treat the boy?

DR. GERALD F. MACHACEK: There are some who state that tuberculids, particularly the papulonecrotic, are influenced for the better by penicillin. I have seen some of these cases but was not convinced of the efficacy of the treatment. Those cases in which there was improvement were probably banal pyogenic chronic granulomas which simulated tuberculids.

DR. H. GOODMAN: How are you going to treat them?

DR. GERALD F. MACHACEK: I would keep the patient on adequate diets under good hygenic conditions and careful supervision.

Bullous Dermatosis. Presented by DR. JESSE A. TOLMACH for DR. GEORGE H. KOSTANT.

This 65-year-old white man was admitted to Beth Israel Hospital on Oct. 9, 1952, approximately four months ago, with a history of an eruption of three weeks' duration. During the previous three years the patient had been given diphenylhydantoin for epilepsy and had been taking three tablets daily for three months prior to admission.

At the time of admission the patient presented an eruption involving the forehead, trunk, and extremities, consisting of erythematous papular papulovesicular and bullous lesions. While some bullae arose on an erythematous base, others did not. There were no mucous membrane lesions.

Two days after his admission typical iris lesions developed on the dorsa of the hands. In view of the development of new lesions cortisone therapy was begun two weeks after the patient's admission and was maintained for five weeks when he was in the hospital. The bullae ceased to erupt after the first week of therapy while he was being given 200 mg. of cortisone daily. The patient was discharged and followed in the outpatient department, a maintenance dose of 125 mg. per day being given. When the dose was reduced to 100 mg. a pruritic eruption broke through on the volar forearms and anterior thighs consisting of grouped bullae. The results of a maintenance dose at a level of 150 mg. daily are satisfactory. Recently moderate edema of the lower extremities has developed.

The laboratory findings were as follows: A biopsy done Oct. 24 revealed a bulla on the left forearm consistent with pemphigus vulgaris and unlikely to be erythema multiforme.

Blood studies gave the following findings: Oct. 9: 13.5 gm. per 100 cc. hemoglobin content, 3,350 white blood cell count, with 69 polymorphonuclear neutrophiles, 2 segmented forms, 22 lymphocytes, 3 eosinophiles, and 4 monocytes; Oct. 27: 11.5 gm. hemoglobin content, 9,050 white blood cell count, with 63 polymorphonuclear neutrophiles, 2 segmented forms, 30 lymphocytes, 3 eosinophiles, and 2 monocytes; Jan. 7, 1953: 13.5 gm. hemoglobin content and 11,900 white blood cell count.

Urinalyses gave normal results.

Blood chemistry studies were as follows: Sugar, 157 mg. per 100 cc. on Oct. 10 and 94 mg. on Oct. 11. Total protein on Oct. 10 was 6.28 gm., with 4.63 gm. albumin and 1.65 gm. globulin (A/G ratio 2.81), and 5.45 gm., with 3.05 gm. albumin and 1.40 gm. globulin (A/G ratio 1.46) on Oct. 23. Sodium was 142/2 mEq. on Oct. 23, 140.8 mEq. Nov. 4; potassium, 4.4 mEq. Oct. 23, 5.4 mEq. Nov. 4.; chlorides, 105.9 mEq. Oct. 23, and 97.9 mEq. Nov. 4.

The electrocardiogram was within normal limits on Oct. 10.

KI.-KBr. patch tests gave negative results.

DISCUSSION

DR. BEATRICE M. KESTEN: The other lesions that I noted were typical purplish polygonal flat papules. It would be my impression that this patient has bullous lichen planus.

DR. DAVID BLOOM: I agree with Dr. Kesten.

DR. MARION B. SULZBERGER: I agree too.

DR. MAX WOLF (by invitation): This seems to be a bullous form of lichen planus. The Köbner phenomenon as observed on the left forearm would support this diagnosis too.

DR. MARION B. SULZBERGER: There are, of course, two varieties of lichen planus with bullae: one called bullous lichen planus and the other lichen planus pemphigoides. They are quite different from each other, because in the bullous lichen planus the lichen planus lesion carries the bullae on its top; whereas in lichen planus pemphigoides the bullae often appear on normal skin, and some of these bullae then turn into lichen planus lesions. There are lichen planus lesions in addition to bullae, but a lichen planus lesion is not inevitably present before the bullae appears at a given site. Pemphigoid lichen planus can be much severer than other forms, and the lichen planus lesion itself can be so much in the background that one really thinks that one is dealing with the bullous erythema multiforme or a pemphigus. Sometimes these patients are, as with pemphigus, rather desperately sick. There is a question in my mind as to whether this patient's case may not belong to the more unusual type of lichen planus pemphigoides. A detailed report on one of these cases was published from our institution a few years ago by Shelton Blair, and the literature was reviewed. There were only a few cases to review.

DR. DAVID BLOOM: This patient has bullous lichen planus. I have no experience with cortisone therapy in lichen planus and cannot, therefore, state whether the persistence of the eruption in this patient is due to poor response to cortisone or to insufficient amount of cortisone.

DR. MARION B. SULZBERGER: The history says that he did benefit from the cortisone; while the dose was up he remained free of lesions. It was only when it was reduced to 100 mg. per day that the lesions broke through again.

DR. JESSE A. TOLMACH: This patient's eruption, originally, was composed of many bullae, some on erythematous bases and some arising from apparently normal skin. A large number of the bullae were hemorrhagic. Mouth lesions were not present. At that time, there were no papules even vaguely suggesting the lichenoid lesions now seen on the flexor surfaces of the forearm and the anterior surface of the thighs. The eruption subsided with treatment with cortisone given orally in daily doses ranging from 150 to 200 mg. At present, the patient is very much improved. The lichenoid papules are of recent origin. The results of two biopsies which have been taken were reported as being suggestive of pemphigus, though dermatitis herpetiformis could not be ruled out. If these present papular lesions are indicative of lichen planus, another biopsy should establish the diagnosis.

DR. MARION B. SULZBERGER: Will you report that, Dr. Tolmach?

DR. JESSE A. TOLMACH: I shall be glad to.

NOTE.—The results of subsequent biopsies from the right forearm and right thigh showed no evidence of lichen planus.

DR. ARTHUR B. HYMAN: The two types of bullous lesions that you described, Mr. Chairman, in lichen planus, translated into histologic terms would give us the two following pictures: In the bullous lichen planus one gets a picture of lichen planus with a bulla immediately under the epidermis; whereas in the condition that you mentioned as lichen planus pemphigoides the bulla may be within as well as under the epidermis and may be found in the epidermis without the typical lichen planus infiltrate. Such sections would be very difficult to interpret as lichen planus. It is only because of associated lesions more characteristic clinically and histologically that the diagnosis could be made in the few cases that I have seen of the lichen planus pemphigoides. In the slides of the condition which I have seen there was an inflammatory reaction that was in no way distinctive. The large number of polymorphonuclear cells and eosinophiles that were seen in the slides of the case here presented do not fit in with pemphigoid lichen planus, so we have no histologic reasons for regarding this as a bullous form of lichen planus; on the other hand, the histologic distinction between pemphigus and dermatitis herpetiformis (Duhring's disease) is, of course, a subject into which one dare not enter at this late hour.

DR. C. T. NELSON: In view of this man's extensive drug intake, should we not consider this a lichen-planus-like drug eruption?

DR. MARION B. SULZBERGER: He has been taking the drug?

DR. JESSE A. TOLMACH: It was stopped two months ago.

DR. MARION B. SULZBERGER: What was it, diphenylhydantoin?

DR. JESSE A. TOLMACH: I only want to add one statement regarding drugs. This man had been taking diphenylhydantoin.. The dose had been increased prior to his admission to the hospital, and the first diagnosis made was a probable drug eruption. However, the drug intake was stopped, and during his hospital stay the lesions cleared up. He was sent to the outpatient department and suffered a severe recurrence, without having resumed taking diphenylhydantoin, so it is hardly likely that that drug was the cause of the recurrence.

Xerostomia (Sjögren's Syndrome?). Presented by DR. JESSE A. TOLMACH for DR. IRVING L. MILLER.

I.B., aged 63, was first seen in December, 1951, with a chief complaint of hair loss of two years' duration. The patient also complained of dryness of the lips, tongue, and buccal mucosa of about two years' duration. There were no complaints referable to the eyes, ears, nose, or throat. Some relief is obtained by sipping small amounts of water frequently. The patient is a known diabetic for the past five years and has been receiving 10 units of insulin daily. Examina-

tion revealed an obese white woman, who presented the following findings: The tongue was of the scrotal type and hobnailed with flattened papillae. Only a few small areas of sticky secretion were usually seen. The buccal mucosa was also dry. The lips were slightly crusted, with some fissuring, and were dry.

Ophthalmological consultation revealed "no evidence of keratoconjunctivitis sicca."

The laboratory data were as follows: The serological reaction for syphilis was negative. The urinalysis gave negative results. The hemoglobin content was 13.6 gm., the red blood cell count 4,100,000, and the white blood cell count 7,000. The urea nitrogen was 11.0 gm. The blood glucose tolerance was 212 mg., 375 mg., 215 mg., and 510 mg. The blood pressure was 180/90 mm. The electrocardiogram was normal.

Treatment was as follows, with no improvement: administration of vitamin A in aqueous solution (Aquasol A), 50,000 units daily, diethylstilbestrol (Stilbestrol), methyltestosterone (Oreton M), and application of estrogen ointment to the scalp.

DISCUSSION

DR. BEATRICE M. KESTEN: The patient only has an extremely dry mouth and a very large tongue. I suggest the diagnosis of amyloidosis.

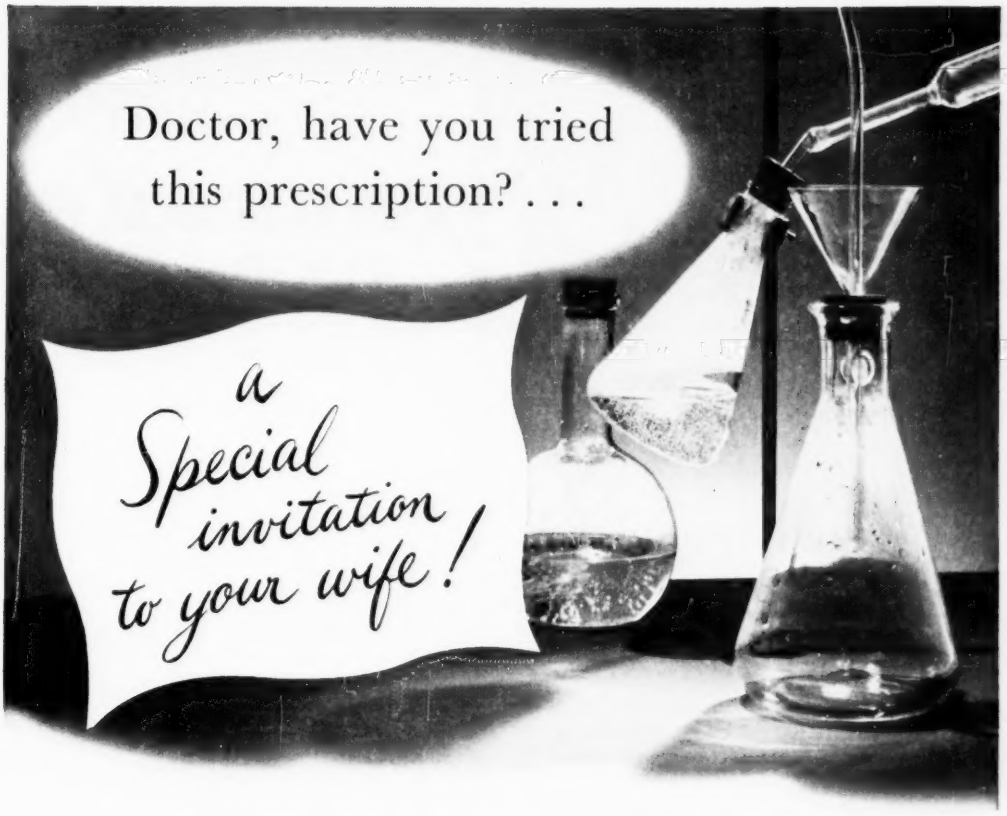
DR. C. T. NELSON: I agree with Dr. Kesten. The scrotal tongue and dry mouth do not make a diagnosis of Sjögren's syndrome. One should also find at least dryness of the conjunctivae as well if one wishes to use this terminology.

DR. HELEN CURTH: In addition to these signs, the patient also has perlèche of both angles of the mouth. She should be thoroughly investigated for avitaminosis or allergy to some contact in the mouth. I want to ask the presenter if the condition of the scalp which I interpret as a very tight scalp has been observed in Sjögren's syndrome.

DR. JESSE A. TOLMACH: This patient certainly has xerostomia. She does not have a lacrimal deficiency. The dryness of the mouth and lips in this case, therefore, may or may not be part of Sjögren's syndrome. Xerostomia is mostly seen in older persons, usually women in the postmenopausal period. Dryness of the mouth may be due to a number of causes, such as drugs, dehydration, vitamin A deficiency, ariboflavinosis, endocrine disturbance, and lymphoblastoma involving the salivary glands. The suggestion of amyloidosis in this case is an interesting one. The patient requires further observation and investigation. At present, any therapeutic suggestions for symptomatic relief will be appreciated.

DR. GERALD F. MACHACEK: To alleviate her symptoms and not as therapy for her condition, which I do not think is clear at the moment, equal parts of glycerin, lemon juice, and water may be applied to her buccal and lingual mucosa.

Cheilitis Glandularis (Presented also for Therapeutic Suggestions). Presented by DR. FREDERICK REISS.
Dermatitis Medicamentosa. Presented by DR. GERALD F. MACHACEK.
Erythema Induratum. Presented by DR. JESSE A. TOLMACH for DR. IRVING L. MILBERG.
Calcinosis. Presented by DR. JESSE A. TOLMACH for DR. GEORGE H. KOSTANT.
Diffuse Lipomatosis. Presented by DR. JESSE A. TOLMACH for DR. LEO ORRIS.
Lupus Erythematosus. Presented by DR. F. P. LOWENFISH for DR. E. WILKISER EHRENREICH.
Hemangioma of Left Side of Face and Neck. Presented by DR. F. P. LOWENFISH.



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3) Modification of formulae, when possible, to eliminate ingredients to which patient demonstrated a sensitivity. (We extend this service to our patrons without extra charge.)

4) Final check tests with modified formulae to make certain there is no reaction.

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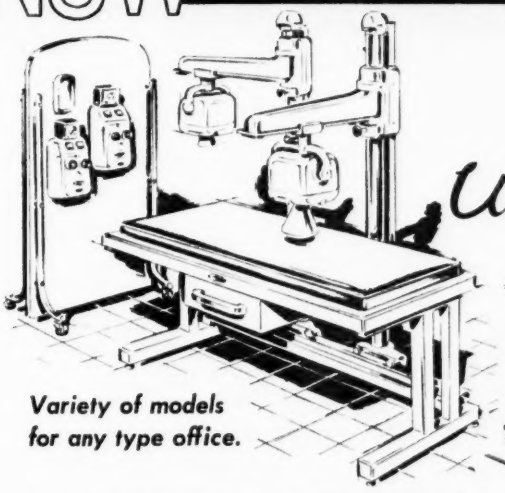

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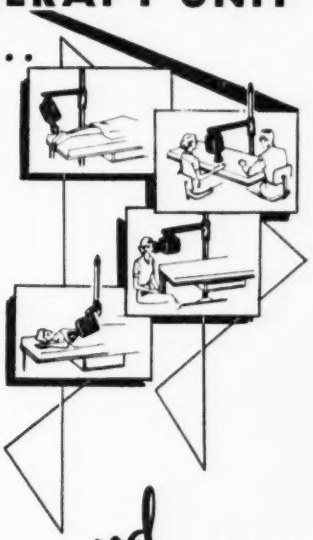

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Archives of Otolaryngology, Sept. 1952: 241-249
The Eye, Ear, Nose & Throat Monthly, April 1950: 200-203
Bulletin of the Johns Hopkins Hospital, Sept. 1948: 225-228
Archives of Otolaryngology, March 1947: 294-297
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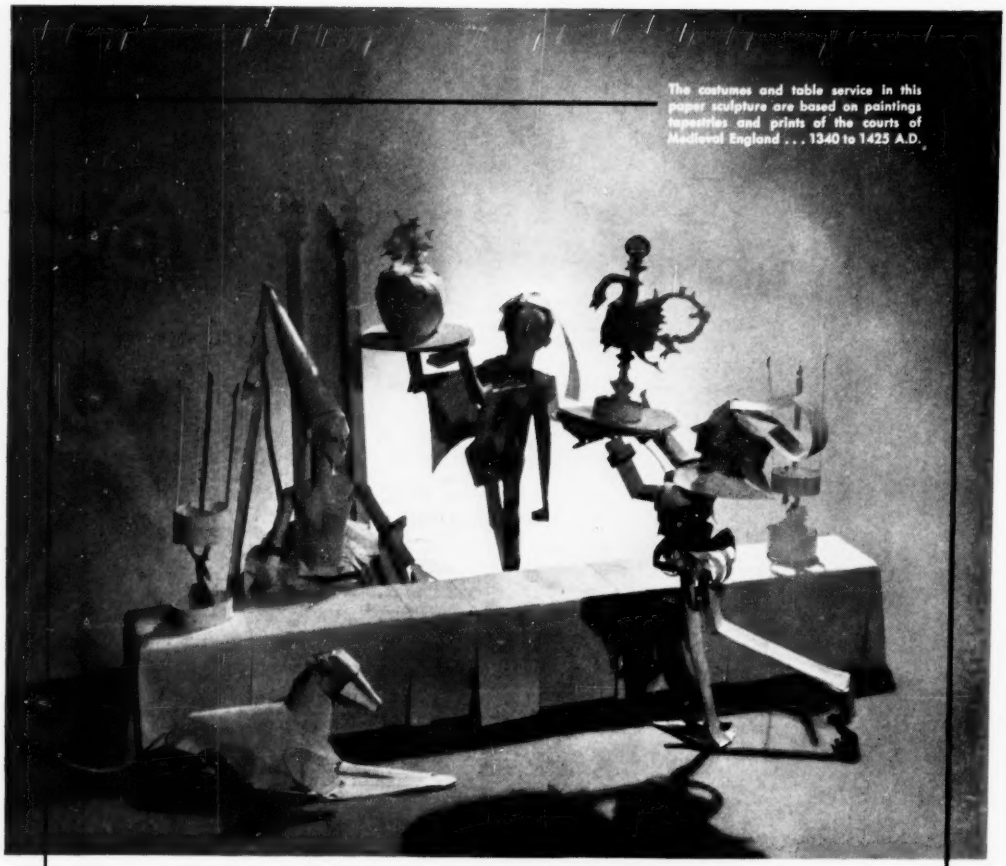
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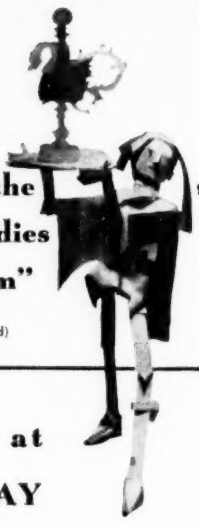

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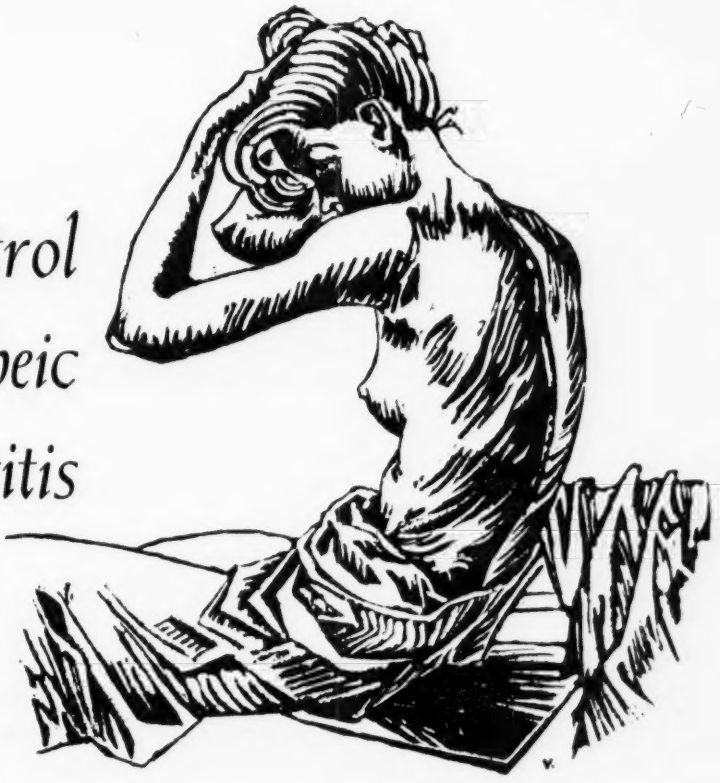

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1. Slepyan, A. H. (1952), Arch. Dermat. & Syph., 65:228, February.
2. Slinger, W. N., and Hubbard, D. M. (1951), *ibid.*, 64:41, July.
3. Sauer, G. C. (1952), J. Missouri M.A., 49:911, November.

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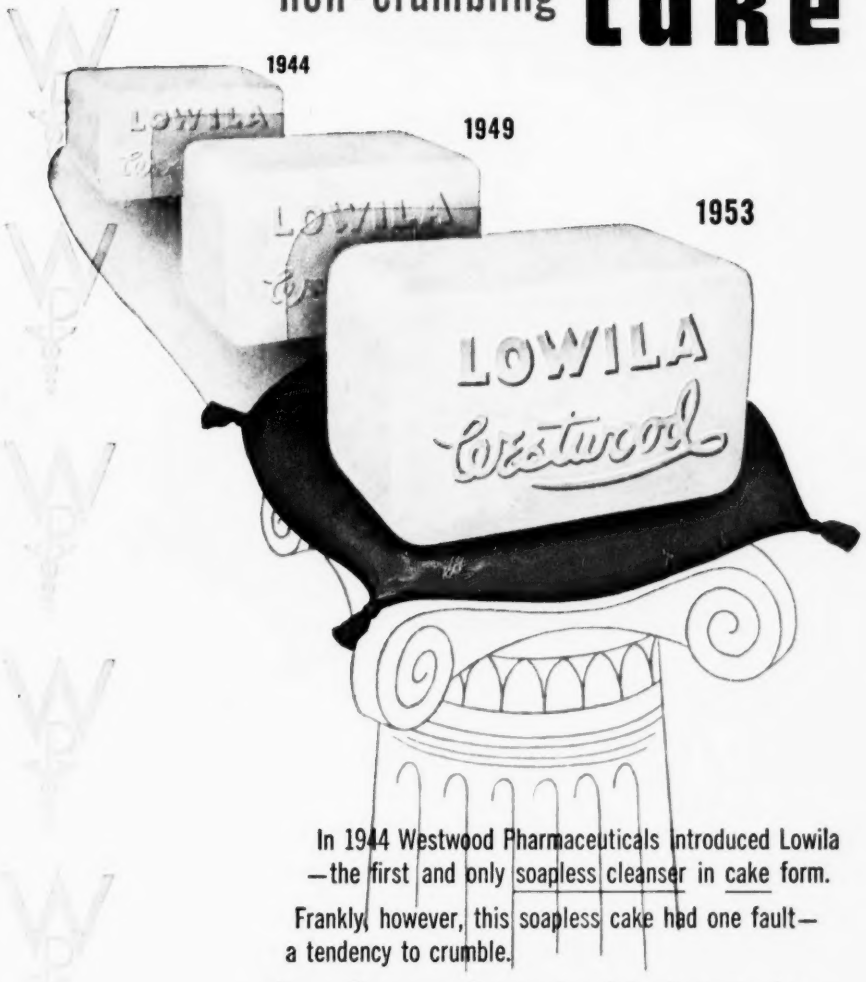

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